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"PRIMARY" HYPOCHROMIC ANEMIA TERMINATING IN PERNICIOUS ANEMIA

REPORT OF TWO CASES

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The possible relation between pernicious anemia and "primary," or "idiopathic," hypochromic anemia has been emphasized in a number of reports. The common denominator in these conditions may lie in a disturbance in the gastric secretion. Castle and his collaborators [1] demonstrated the importance of a defect in gastric secretion in the pathogenesis of pernicious anemia. Davies,[2] Dameshek,[3] Hartfall and Witts [4] and others found either complete achlorhydria or distinct hypoacidity in the great majority of their cases of "primary," or "idiopathic," hypochromic anemia. It has, furthermore, been noted that complete gastrectomy or a widespread malignant condition of the stomach is not

From the Joseph H. Pratt Diagnostic Hospital and the Blood Clinic, Boston Dispensary.

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1. Castle, W. B.; Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: IV. A Biologic Assay of the Gastric Secretion of Patients with Pernicious Anemia Having Free Hydrochloric Acid and That of Patients Without Anemia or with Hypochromic Anemia Having No Free Hydrochloric Acid, and of the Role of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, Am. J. M. Sc. **182**:741, 1931.

2. Davies, D. T.: Studies on Achlorhydria and Anemia, Quart. J. Med. **24**: 447, 1931.

3. Dameshek, W.: (*a*) Primary Hypochromic Anemia (Erythro-Normoblastic Anemia): A New Type of Idiopathic Anemia, Am. J. M. Sc. **182**:520, 1931; (*b*) Primary Hypochromic Anemia: II. Clinical Features, J. A. M. A. **100**:540 (Feb. 25) 1933.

4. Hartfall, S. J., and Witts, L. J.: Gastric Secretion in Simple Achlorhydric and Allied Anemias, Guy's Hosp. Rep. **83**:3, 1933.

infrequently followed by the development of either the "liver extract" deficiency or the iron deficiency type of anemia.[5]

The relation between pernicious anemia and "primary" hypochromic anemia was first suspected when it was noted that achlorhydria was often familial.[6] It was occasionally reported that one or more members of a family had pernicious anemia while others showed hypochromic anemia.[7] The second, and more direct, line of evidence is presented in the sporadic reports by various observers [8] of idiopathic hypochromic anemia which has terminated in pernicious anemia. In addition, Buchgraber and Fleischhacker [9] observed a case of gastric resection in which after fifteen years of hypochromic anemia responding well to iron pernicious anemia developed which was controlled by liver extract therapy. Definite evidence of the transition of one state to another is often difficult to establish, either because the descriptions of the hypochromic anemia are meager or because complications, such as hemorrhage or a malignant condition, may give a hypochromic picture to the otherwise macrocytic character of pernicious anemia.[10]

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5. (*a*) Morawitz, P.: Agastrische Anämien und ihre Beziehungen zur Anaemia perniciosa, Arch. f. Verdauungskr. **47**:305, 1930. (*b*) Planteydt, J. M.: Transition of Hypochromic into Hyperchromic Anemia Many Years After Gastric Resection, Nederl. tijdschr. v. geneesk. **79**:4153, 1935. (*c*) Hurst, A. F.: Achlorhydria and Achylia Gastrica, and Their Connection with Addison's Anemia—Subacute Combined Degeneration Syndrome and Simple (Non-Addisonian) Achlorhydric Anemia. Quart. J. Med. **1**:157, 1932.

6. (*a*) Oliver, T. H., and Wilkinson, J. F.: Achlorhydria, Quart. J. Med. **2**:431, 1933. (*b*) Wilkinson, J. F., and Brockbank, W.: The Importance of Familial Achlorhydria in the Aetiology of Pernicious Anemia, ibid. **24**:219, 1931. (*c*) Gram, H. C.: Further Observations on a Family Showing Many Cases of Pernicious Anemia, Acta med. Scandinav., 1930, supp. 34, p. 107. (*d*) Hartfall and Witts.[4] (*e*) Hurst.[5c]

7. (*a*) Heath, C. W.: The Interrelation of Pernicious Anemia and Idiopathic Hypochromic Anemia, Am. J. M. Sc. **185**:365, 1933. (*b*) Sinkler, W., and Eshner, A. A.: Three Cases of Essential Anemia in One Family—Father and Two Daughters, ibid. **112**:287, 1896. (*c*) Patek, A. J.: Family Pernicious Anemia. J. A. M. A. **56**:1315 (May 6) 1911. (*d*) Bartlett, C. J.: Family Pernicious Anemia, ibid. **60**:176 (Jan. 8) 1913. (*e*) Maclacklan, W. W. G., and Kline, F. M.: The Occurrence of Anemia in Four Generations, Am. J. M. Sc. **172**:533. 1926. (*f*) Hartfall and Witts.[4] (*g*) Hurst.[5c] (*h*) Wilkinson and Brockbank.[6b] (*i*) Gram.[6c]

8. (*a*) Schulten, H.: Ueber die essentielle (primäre) hypochrome Anämie. München. med. Wchnschr. **85**:1599, 1938. (*b*) Witts, L. J.: Simple Achlorhydric Anemia, Guy's Hosp. Rep. **80**:253, 1930. Dameshek.[3b] Hartfall and Witts.[4] Gram.[6c] Heath.[7a]

9. Buchgraber, K., and Fleischhacker, H.: Uebergang einer hypochromen Resektionsanämie in Perniziosa, Wien. Arch. f. inn. Med. **32**:33, 1938.

10. (*a*) Hurst, A. F., and Bell, J. R.: The Pathogenesis of Subacute Combined Degeneration of the Spinal Cord, with Special Reference to Its Connection with

The present report deals with 2 cases of "primary," or "idiopathic," hypochromic iron-deficiency anemia which terminated in pernicious anemia. In the first case, in which the Plummer-Vinson syndrome was present and the response to iron was good, typical pernicious anemia responding to liver extract developed several years later. In the second case, which was apparently an instance of typical primary hypochromic anemia, pernicious anemia developed after the administration of iron; in this case, apparently both iron deficiency and liver extract deficiency were simultaneously present, and the administration of iron "unmasked" the underlying macrocytic anemia. The implications of these transitions are discussed.

REPORT OF CASES

CASE 1.—*First Admission.* Lillian D., a 40 year old widow, was admitted to the diagnostic ward of the Boston Dispensary on Jan. 17, 1933, because of weakness and anemia. As a girl, she had been known to have a sallow complexion but was never told she was anemic. She became extremely nervous on the death of her husband, which occurred in 1925, only two years after their marriage. Since 1925, transitory periods of dysphagia occurred, increasing in frequency when she became a secretary for an exacting employer. About five years before her admission to the ward, inability to swallow solid food developed, and her diet became limited to eggs, milk, mush, mashed potatoes and cooked fruit. The patient confessed later that she had an intense dislike for meat even prior to the development of dysphagia because of the thought of the animals being slaughtered. It was also established that one of her nieces, who had a sallow complexion, possessed an aversion to meat and that a first cousin had been treated at another hospital for dysphagia and hypochromic anemia. When the patient was 35, her hair began to turn gray and her finger nails became brittle; the latter symptom was especially troublesome because of her work with the typewriter. Weakness, palpitation, swelling of the ankles and dyspnea on exertion developed. Finally, when pallor became noticeable, about two years before admission, she consulted a physician, who told her she was anemic. Later, diarrhea developed, with five to seven loose stools daily, and a burning sensation of the tongue was felt when fruit juices were taken. During the past four to five years she had noticed that her tongue was often unnaturally red, and during the few months before admission excoriations developed at the angles of the mouth and the tongue became increasingly sore. Until a few years previous to admission her menses had always been regular, but shortly before entry they had become delayed and scant. Paresthesias of the fingers and hands developed in November 1932. About one month previously she had noticed black stools for three days. On admission to the diagnostic ward of the Boston Dispensary on Jan. 17, 1933, and later to the medical ward of the Beth Israel Hospital,[11] on January 23, she was found to be pale, with a sallow, parchment-colored skin. There was, however, no icterus. The

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Addison's (Pernicious) Anemia, Achlorhydria and Intestinal Infection, Brain **45**: 266, 1922. (*b*) McGregor, H. G.: Pernicious Anemia with Diabetes Mellitus, Brit. M. J. **2**:617, 1937. (*c*) Thyasen, T. E. H.: Ein Fall perniziöser Anämie mit ungewöhnlichen Verlauf, Klin. Wchnschr. **7**:1330, 1928.

11. The director of Beth Israel Hospital gave us permission to report the data in this case, which was studied during the senior author's service at that hospital.

hair, which was dyed black, was fundamentally gray. The tongue was completely devoid of coat and papillae and was extremely shiny; it was definitely atrophied and greatly reddened in several areas. At the angles of the mouth, superficial excoriations (*la perlèche*, or cheilosis [12]) were present. The heart was not enlarged; a systolic murmur was present at the apex. The liver and spleen were not felt. The reflexes were normal, and there was no disturbance in the vibration sense. All the finger nails showed vertical ridging; a few were flattened, but there was no definite spooning.

The laboratory data were as follows: The urine gave a negative reaction for albumin and sugar; the fecal urobilinogen content was not increased; four stools gave negative reactions for ova, parasites and occult blood; the Wassermann, Kahn and Hinton reactions of the blood were negative. The blood count showed: hemoglobin concentration, 32 per cent (Sahli); red cells, 4,000,000 per cubic millimeter; white cells, 10,200; platelets, 400,000, and reticulocytes, 2.6 per cent. The red cells showed considerable achromia, with moderate variation in size and shape (fig. 1 *A*). They varied in diameter from 4.5 to 10.5 microns, the average cell diameter being 6.90 microns (fig. 2 *I*). The red cells were more hypochromic than microcytic. Most of the polymorphonuclear cells had three to six nuclear lobes. The icteric index was 6; the level of serum proteins, 6.08 Gm. per hundred cubic centimeters. The gastric analysis showed an extreme diminution in secretion, with complete achlorhydria after the administration of histamine phosphate.

Time Elapsed After Injection of 1 Cc. of Histamine Phosphate (Minutes)	Volume, Cc.	Free Hydrochloric Acid	Total Acid	Lactic Acid	Guaiac
0 (fasting)	5	0	10	0	0
20	10	0	12	..	0
40	1	0	14	..	0
60	1	0	12	..	0
80	5	0	18	..	0

Roentgenograms of the gastrointestinal tract showed slight delay of the barium sulfate meal in the esophagus and a questionable irregularity at the junction of the pharynx with the esophagus. The upper one third of the esophagus showed slight spasm. The remainder of the roentgen examination revealed nothing abnormal.

The diagnosis of primary hypochromic anemia with the Plummer-Vinson syndrome was made.

Clinical Course (fig. 3): During the first ten days of the patient's stay at the Beth Israel Hospital, she was given, in addition to a bland diet, the extract from 1 pound (0.45 Kg.) of meat daily, with little or no response. During the next six day period the patient received 150 Gm. of powdered hemoglobin daily. This medication was discontinued because of severe diarrhea. During the next eight days fresh whole beef blood obtained from the slaughterhouse was given in amounts of 250 cc. four times daily. At the end of this twenty-four day period the blood picture was essentially unchanged, although there had been a slight rise in hemoglobin (hemoglobin concentration 43 per cent, red blood cells 4,200,000). There was no definite reticulocyte response. At this point the patient was given 8 Gm. of ferric ammonium citrate daily for ten days; there was no

12. These lesions are as characteristic of a chronic iron deficiency as they are of riboflavin deficiency, although they have recently been stated to be pathognomonic of the latter.

response to this medication, the hemoglobin concentration being 45 per cent and the red cell count 4,440,000 at the end of the period. The iron was continued, but in addition 20 mg. of copper sulfate was administered daily during the next twelve days. With this regimen, the hemoglobin concentration rose to 56 per cent and the red cell count to 4,300,000. By this time, the patient had gained

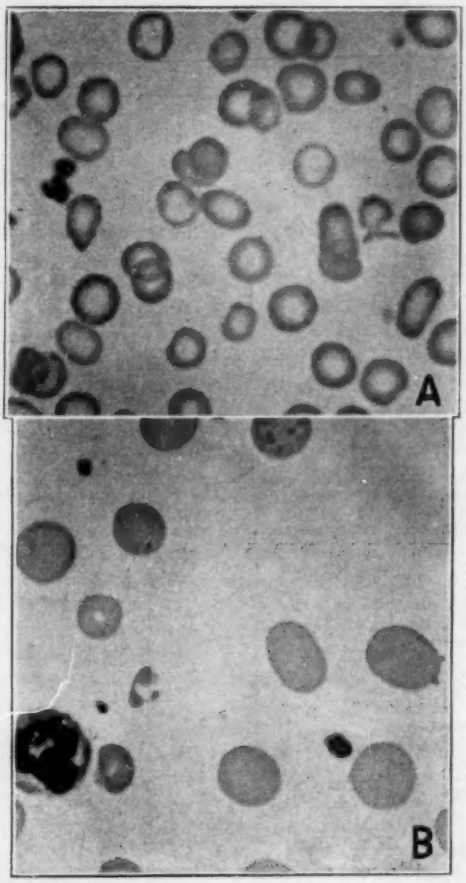

Fig. 1 (case 1).—*A*, photomicrograph of a blood smear (× 1,000) made Jan. 23, 1933 (hemoglobin concentration 23 per cent, red cell count 4,000,000). Note that the red cells are hypochromic and that many are microcytic. *B*, photomicrograph of a blood smear (× 1,000) made April 26, 1939, when pernicious anemia was evident (hemoglobin concentration 34 per cent, red cell count 1,260,000). Note that the red cells are well filled with hemoglobin and tend to be of large size. A granulocyte with a multilobulated nucleus is seen.

8 pounds (306 Kg.) and felt much stronger; the diarrhea had completely disappeared, and the dysphagia had lessened considerably. She was discharged on March 13 on a full house diet, together with 8 Gm. of ferric ammonium citrate and 20 mg. of copper sulfate daily.

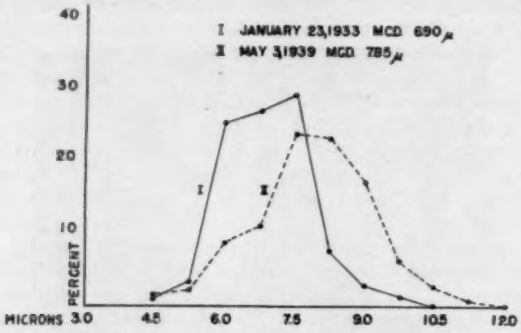

Fig. 2 (case 1).—Price-Jones curves of red cell diameters in the hypochromic (*I*) and the macrocytic (*II*) stage. It should be noted that, although the color index in the hypochromic stage is extremely low (tabulation), the erythrocytes which are 7.5 microns or over represent more than 40 per cent of the red cell population. This might indicate a beginning tendency even at this time for the development of macrocytosis (*II*). *M. C. D.* indicates mean cell diameter.

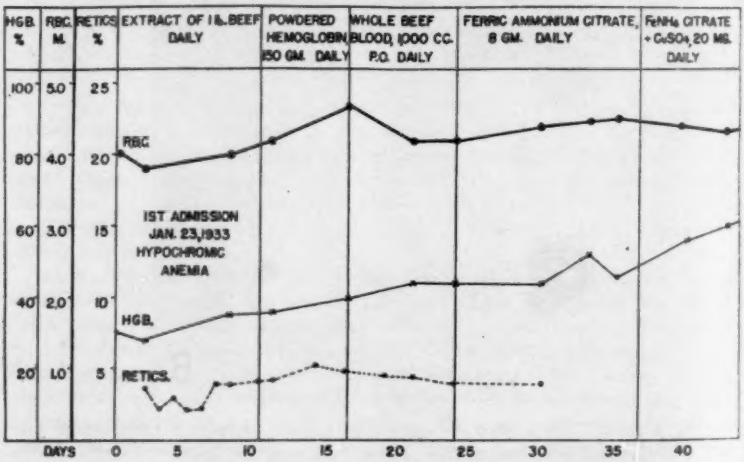

Fig. 3 (case 1).—Hematologic course during the stage of "primary" hypochromic anemia in January and February 1933. There was a slight response to beef extract, powdered hemoglobin and whole beef blood, no further response when large doses of ferric ammonium citrate were given, but a definite response when copper sulfate was added to the iron medication. Note the wide discrepancy between the red cell and the hemoglobin level (low color index).

The patient was seen frequently until September 1933. The red cell count and the hemoglobin concentration remained at about 4,500,000 to 4,800,000 and 60 to 65 per cent, respectively. She continued to feel well and gained weight slowly. The lesions at the corners of the mouth had healed with some scarring, and the nails had lost their vertical striations and flattening and were now completely convex. The dysphagia had lessened considerably, and she was able to eat ground meat despite her dislike for it. The medication was decreased to 5 Gm. of ferric ammonium citrate and 10 mg. of copper sulfate daily. She returned to the clinic in May 1934, stating that she had discontinued her medication during the past eight months. She was eating solid meat and green vegetables once daily, felt well and had continued to gain weight slowly. In October 1934, although she had not taken iron for almost a year, the hemoglobin concentration was 75 per cent. Except for an atrophic tongue, the examination showed nothing significant.

She did not return to the clinic until June 1936. At this time she stated that during the previous six months her symptoms had returned, and there were increasing diarrhea and dysphagia. Examination revealed pallor and a red, atrophic tongue. Neurologic examination showed nothing abnormal. The red blood cell count was now 2,880,000 and the hemoglobin content 71 per cent! One month later examination of the blood showed the red cell count to be 3,220,000, the hemoglobin concentration 77 per cent, the white cell count 6,800, the reticulocyte percentage 1.1, the hematocrit reading 35 per cent, the mean corpuscular volume 109 cubic microns and the average cell diameter 8.10 microns. The icterus index was 10. At this time, the diagnosis of pernicious anemia was made, but when hospitalization was advised the patient disappeared from observation until almost three years later.

Second Admission (May 3, 1939).—During the nine months preceding this admission there had been an increase in the dysphagia and a return of exertional dyspnea, together with swelling of the ankles. The skin had become increasingly pale and more yellowish in appearance. The patient had gradually lost 15 pounds (6.8 Kg.). Because of the dysphagia, she had eaten little meat.

The essential physical findings were as follows: extreme pallor, bilateral posterior cataracts; perforated nasal septum; atrophic glossitis; perlèche at the left side of the mouth; a just palpable liver edge; a systolic murmur at the apex; minimal pitting edema of the ankles; normal finger nails. Vibration sense over the ankles and tibias was diminished, although the reflexes and the gait were normal.

Laboratory Data: Several specimens of urine were normal. Examination of the blood showed: red cells, 1,260,000; hemoglobin concentration, 34 per cent; white cells, 4,400; reticulocytes, 2.0 per cent, and platelets, 270,900. The stained smear showed microcytosis and macrocytosis, and multilobulated leukocytes were present (fig. 1 *B*). Price-Jones diameter curves showed a definite macrocytosis (fig. 2 *II*). The icterus index was 14. Although there was still complete achlorhydria, the gastric analysis now showed essentially normal volumes, as compared with the extremely low volumes recorded several years previously:

Time Elapsed After Injection of 1 Cc. of Histamine Phosphate (Minutes)	Volume, Cc.	Free Hydrochloric Acid	Total Acid	Lactic Acid	Guaiac
0 (fasting)	14	0	6	0	3+
20	2	0	..	..	0
40	71	4	..	..	1+
60	25	0	3	..	0

Roentgenograms of the gastrointestinal tract showed nothing abnormal, except slight flattening of the greater curvature aspect of the stomach, due apparently to pressure from a slightly enlarged spleen. A sternal puncture showed the typical findings of pernicious anemia, i. e., megaloblastic hyperplasia, with numerous "giant" metamyelocytes.

Clinical Course (fig. 4): In addition to a bland diet, the patient was given tablets of ferrous sulfate in doses of 12 grains (0.78 Gm.) daily for eleven days. At the end of this period there was essentially no change in the blood count; the red cell count was 1,400,000, the hemoglobin concentration 38 per cent and the reticulocyte percentage 4. She was then given liver extract intramuscularly in doses of 1 U. S. P. unit daily for eleven days, after which 6 U. S. P. units of liver extract was given. The peak reticulocyte response was obtained on the twelfth day of liver therapy, when the reticulocyte percentage was 18.

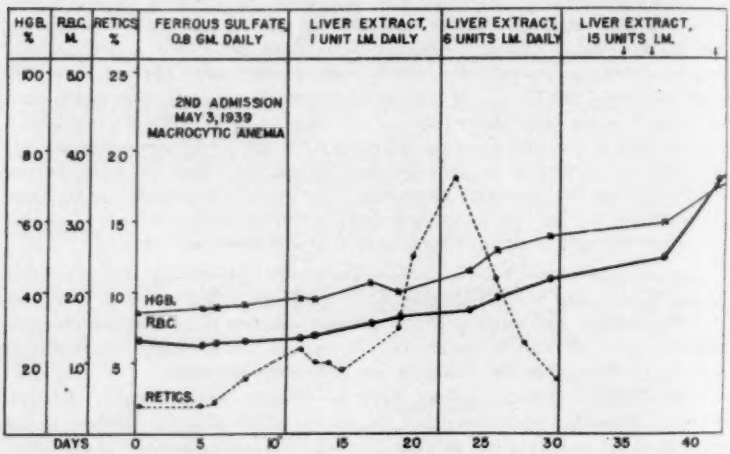

Fig. 4 (case 1).—Hematologic course during the stage of pernicious anemia in May and June 1939. There was a possible slight reticulocyte rise following iron medication, a definite reticulocyte response to 1 U. S. P. unit of liver extract given intramuscularly, followed by a satisfactory erythrocyte increase when larger doses of liver extract were given. Note the high relative concentration of hemoglobin as compared with the red cell count (high color index).

During the next two months, with continued parenteral liver extract therapy, the anemia showed consistent improvement so that on Aug. 4, 1939 the red cell count was 4,550,000 and the hemoglobin concentration was 80 per cent. The patient felt stronger and had gained 5 pounds (2.3 Kg.) in weight. Dysphagia was still present. There was improvement in the vibration sense. The icterus index was 6.

With the continued administration of liver extract, the patient's blood counts have been maintained at normal levels. Dysphagia has continued and has caused great embarrassment in the patient's work as a practical nurse on account of the length of time she requires in eating a meal. Roentgenograms made with a special technic at the Pratt Diagnostic Hospital (Dr. Alice Ettinger, roentgenologist) on

Feb. 4, 1941 revealed two asymmetric indentations of the cervical portion of the esophagus, one about 1 cm. below the other. Above the indentations the passage of the barium meal was somewhat delayed and slight retention was present (fig. 5).

Comment on Case 1.—Course: As a girl, the patient had been sallow and might have been anemic, although this condition is not definitely known to have existed. The chronologic development of symptoms in this case may be tabulated as follows:

Date	Subjective Symptoms	Objective Symptoms	Blood Findings	Diagnosis
Adolescence 1925 (age 32)	Dislike for meat; death of husband; extreme nervousness; transitory dysphagia	"Sallow"		
1928 (age 35)	"Tyrannic" employer; severe dysphagia; great limitation of diet; dyspnea; palpitation; edema of ankles	Hair beginning to gray; brittle finger nails; red tongue		
1931 (age 32) 1932	Diarrhea; burning tongue increasing symptoms; paresthesias; scanty catamenia	Pallor	.....	Anemia
1933 (age 40)	.....	Pallor; glossitis; cheilosis; finger nail changes; gray hair; delayed passage apparent in roentgenograms of esophagus; achlorhydria; small volume of gastric juice; excellent response to therapy with iron and copper	Hemoglobin concentration 33 per cent; red cell count 4,000,000; color index less than 0.5; mean corpuscular diameter 6.90 microns	Primary hypochromic anemia
1933-1934	Improvement	Atrophic tongue	.....	Hypochromic anemia in remission
1935	.....	Disappearance from observation		
1936	Weakness; diarrhea; dysphagia	Pallor; glossitis	Hemoglobin concentration 77 per cent; red cell count 3,220,000; mean corpuscular volume 109 cubic microns	Pernicious anemia
1937-1938	.....	Disappearance from observation		
1939	Weakness; diarrhea; dysphagia	Pallor; glossitis; subicterus; diminished vibratory sensation; achlorhydria	Hemoglobin concentration 34 per cent; red cell count 1,260,000; color index 1.35	Pernicious anemia
1939	Improvement (good response to liver extract; no response to iron)	Glossitis	Hemoglobin concentration 88 per cent; red cell count 4,500,000	Pernicious anemia in remission
1940-1942	Dysphagia	Roentgenographic evidence of "sideropenic dysphagia"		

In our experience, aversion to meat is a common symptom in cases of both pernicious anemia and "primary" hypochromic anemia. In the case at hand, it appears to have been based on psychic grounds, although occurrence of a similar condition in a niece, as well as the presence of the Plummer-Vinson syndrome

in a cousin, make one suspect a constitutional factor. It is possible that in the presence of achlorhydria there is a greatly reduced craving for meats, which in some cases may develop into an actual aversion.

In most cases of the so-called Plummer-Vinson syndrome (which is simply "primary" hypochromic anemia in association with dysphagia) there is no clearcut history indicating whether the dysphagia antedated the anemic state or vice versa. In the present case, dysphagia first appeared during a serious emotional crisis and grew worse with continued psychic distress. It was followed in due course by severe restriction of solid meat and other iron-containing food and by the symptoms of a deficiency state, namely, diarrhea, glossitis, cheilosis, paresthesias and anemia. It is likely that the constitutional background of achlorhydria and the "psychosomatic" factors just mentioned were probably jointly responsible for the development of the iron deficiency state ("primary," or "idiopathic," hypochromic anemia) which was diagnosed in 1933 and which responded well to the adminis-

Fig. 5 (case 1).—Roentgenogram (reduced) of the upper part of the esophagus taken with thick barium sulfate paste according to the spot film technic. The picture is typical of that obtained in cases of the Plummer-Vinson syndrome and shows two asymmetric indentations in the cervical portion of the esophagus. There are slight delay in the passage of the barium and slight retention above the first indentation.

tration of iron. In 1933, all the typical features of this state, as described by Witts,[8b] Dameshek,[3] Wintrobe and Beebe [13] and others, were present. These features included considerable sallow pallor without icterus, gray hair, perlèche (cheilosis), atrophic glossitis, complete histamine achlorhydria and probable esophageal changes.

In 1936, however, three years later, the blood picture had become completely modified from that of a hypochromic, microcytic variety of anemia to a hyperchromic, macrocytic type, and the diagnosis of pernicious anemia was made. This was substantiated when the patient continued to relapse and become seriously anemic in 1939. At this time, the bone marrow was megaloblastic; there was failure of response to iron, but there was an excellent response to liver extract.

13. Wintrobe, M. M., and Beebe, R. T.: Idiopathic Hypochromic Anemia. Medicine **12**:187, 1933.

It appears, therefore, that in this patient there was definite transition from a typical iron deficiency state, with chronic hypochromic microcytic anemia responding to iron, to a typical "liver extract" deficiency state, with chronic hyperchromic macrocytic anemia responding to liver extract. The theoretic implications involved in this transition are of great interest.

The persistence of dysphagia and of the characteristic roentgenographic signs of the Plummer-Vinson syndrome is of some importance. According to Waldenström and Kjellberg,[14] these findings in a case of pernicious anemia may serve as landmarks indicating the previous existence of an iron deficiency state. Anemia is almost always present in the Plummer-Vinson syndrome and, except in 3 recorded instances, has been of the hypochromic type. In the case reported by Croskery,[15] dysphagia was present in association with pernicious anemia; however, the patient was anemic as a girl and, as Waldenström and Kjellberg pointed out, probably had an iron deficiency state at that time. In 2 cases reported by the latter authors, although typical pernicious anemia was present, the serum iron was low, indicating a possible iron deficiency as well. In no previous case of the Plummer-Vinson syndrome has the definite transition from hypochromic anemia to pernicious anemia been recorded. Waldenström and Kjellberg propose the term sideropenic dysphagia for the nondescript term of Plummer-Vinson syndrome.

CASE 2.—Mabel K., a 35 year old housewife, was referred to the Joseph H. Pratt Diagnostic Hospital on Aug. 12, 1940 from the Blood Clinic of the Boston Dispensary, primarily for study of her anemia. She had been weak and tired for many years. Her childhood had been spent in orphanages, where she had never had much to eat. She recalled having taken iron medication in her early years.

She was married at the age of 16, and again at 19, with four resulting pregnancies. Two children were living and well, and the other two died in infancy, of pneumonia and intussusception. Twelve years before admission she was ill for six weeks with abdominal pain on urination and had similar complaints three years later when she was eight and a half months pregnant. Seven years previously, she was advised to take iron because of anemia.

Her diet had been poor for many years. Analysis of the dietary intake revealed that it was high in starches and low in proteins, fats, minerals and vitamins A, C and D and the B complex. It was not unusual for her to go without meat for a month at a time. In addition, her appetite was usually poor, so that the total caloric intake was low and was roughly calculated as 1,500 to 1,600 calories per day.

The menses began at the age of 15 and had always been regular, lasting four to five days. They had never been profuse. During the year before admission they appeared every three weeks and lasted one to six days. Although the presence of hemorrhoids was known, there had never been any grossly bloody or tarry stools. Specific symptoms, such as burning of the tongue, brittleness or spooning of the finger nails, paresthesia of the hands or feet and jaundice or dysphagia were lacking. No history of familial anemia could be elicited.

On admission to the hospital, the patient was found to be underdeveloped and undernourished, weighing but 95½ pounds (43.6 Kg.). The skin was parchment

14. Waldenström, J., and Kjellberg, S. R.: The Roentgenological Diagnosis of Sideropenic Dysphagia, Acta radiol. **20**:618, 1939.

15. Croskery, S. E.: Dysphagia Associated with Anemia, Brit. M. J. **1**:494, 1928.

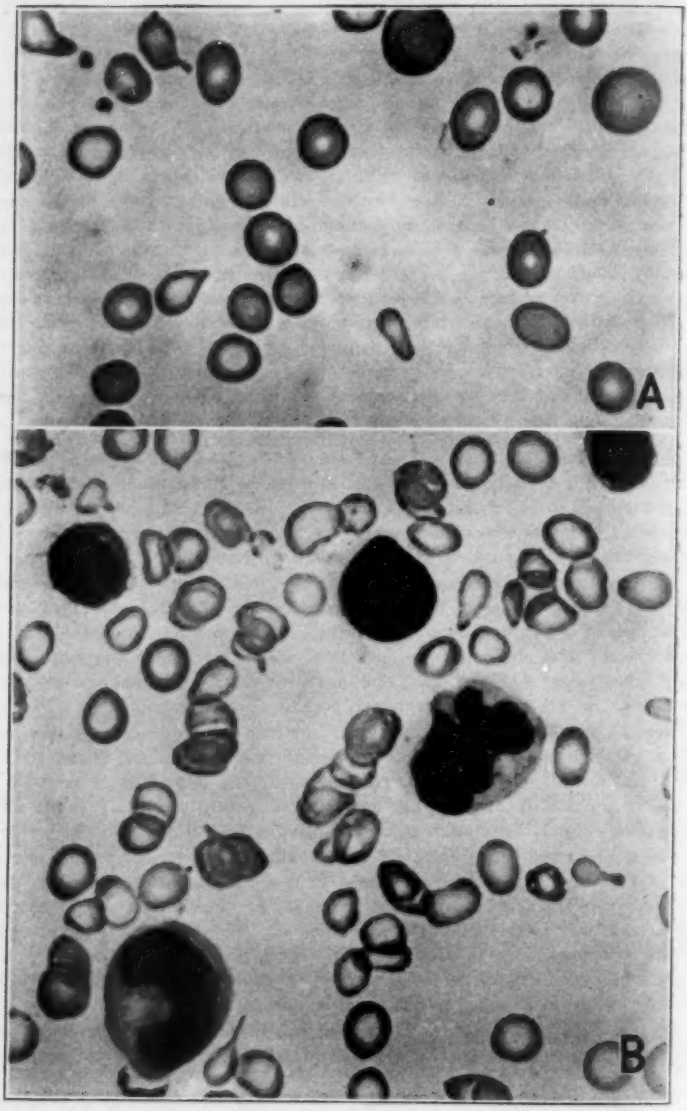

Figure 6

(See legend on opposite page)

pale and without icterus. There was bilateral angular stomatitis (cheilosis), with long reddened fissures about 1 cm. in length, surrounded by scaling skin. The tongue was smooth, glistening and atrophic. The hair and the finger nails were normal. Examination of the heart revealed that the second aortic sound was somewhat accentuated, and the blood pressure was 150 mm. of mercury systolic and 84 mm. diastolic. The liver and the spleen could not be felt. The right knee jerk was somewhat diminished, but the left knee jerk and the ankle jerks were normal; position and vibratory sense were unimpaired.

The laboratory data were as follows: The urine gave a slightly positive reaction for albumin; the sediment showed a few epithelial cells and 3 to 5 leukocytes per high power field. Culture from a catheterized specimen was sterile. The phenolsulfonphthalein test of renal function showed excretion of 64 per cent in two hours. Three stools were negative for ova, parasites and occult blood. The fecal urobilinogen content (daily average output) was 41.2 mg., and the "hemolytic index" was 21.8 (somewhat higher than the usual value, in hypochromic anemia, of less than 10). The Wassermann, Kahn and Hinton reactions of the blood were negative. The blood counts showed: hemoglobin concentration, 38 per cent; red cell count, 2,700,000 per cubic millimeter, and white cell count, 4,300; platelets, 239,000, and reticulocytes, 3.7 per cent. On the smear, the red cells were of two types; most were slightly microcytic and moderately hypochromic, but a few were macrocytic, with a full complement of hemoglobin (fig. 6*A*). The diameters of the red cells varied from 5.3 to 10.5 microns (fig. 7*I*), the average being 6.95 microns. The mean corpuscular volume was 87.3 cubic microns. Gastric analysis showed complete achlorhydria after subcutaneous injection of histamine phosphate.

Time Elapsed After Injection of 1 Cc. of Histamine Phosphate (Minutes)	Volume, Cc.	Free Hydrochloric Acid	Total Acid	Lactic Acid	Guaiac
0 (fasting)	38	0	4	0	0
10	3	0	10	0	0
20	3	0	5	0	0
30	3	0	10	0	0
40	3	0	15	0	0

Roentgenograms of the gastrointestinal tract were completely normal. Gastroscopic examination revealed a pale mucosa, without evidence of atrophy. In the body on the anterior wall was a localized area, 4 by 5 cm., consisting of convoluted,

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EXPLANATION OF FIGURE 6

Fig. 6 (case 2).—*A*, photomicrograph of a blood smear (× 1,000) made Aug. 12, 1940, when the hemoglobin concentration was 38 per cent and the red cell count 2,700,000 per cubic millimeter. Note that, although the cells are generally small and hypochromic, a few definite well hemoglobinized macrocytes are present. *B*, photomicrograph of a bone marrow smear (× 1,000) made Aug. 13. Note the background of hypochromic red cells, the two "giant" metamyelocytes with bizarre nuclei and the three megaloblasts with scanty cytoplasm. Although the anemia was hypochromic, the bone marrow picture was sufficiently like that of pernicious anemia to make one venture the suggestion that a transition to the latter disease might occur.

moundlike patches, each of which measured about 0.5 by 0.5 cm. Puncture of the sternal bone marrow showed the following differential count: [16]

Type of Cell	Percentage	Type of Cell	Percentage
Myeloblasts	0.0	Erythrogones	4.2
Myelocytes	9.0	Megaloblasts A	5.4
Metamyelocytes	2.4	Megaloblasts B	14.4
"Giant" metamyelocytes	23.6	Megaloblasts C	9.4
Mature granulocytes	8.4	Normoblasts A	0.6
Eosinophils	0.2	Normoblasts B	6.0
Histiocytes	0.4	Normoblasts C	16.0

The megaloblasts were unusual, not only because of their presence in hypochromic anemia but because of their appearance, for the nuclei were typically "scroll-like" [16] but the cytoplasm was scanty.

The clinical diagnosis was that of hypochromic anemia due to iron deficiency and possibly in some measure to a vitamin B deficiency state. The few following atypical features were, however, present: a normal mean corpuscular volume

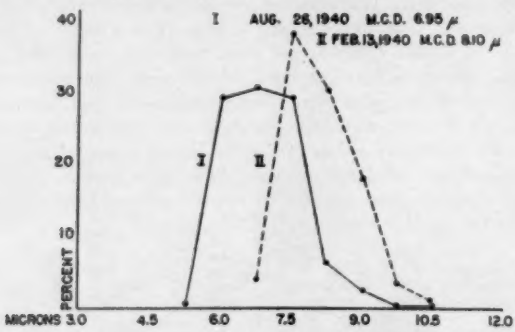

Fig. 7 (case 2).—Price-Jones curves of red cell diameters during the hypochromic, microcytic stage (*I*) and the macrocytic stage (*II*). Note the presence of macrocytes during the microcytic stage and the shift to larger cells when iron was given. The iron was apparently responsible for the complete disappearance of the microcytosis (see also figure 9 *A*).

despite the hypochromia and the low color index; a fair number of macrocytes; the condition of the marrow, which showed bizarre giant metamelocytes and megaloblasts, and the slightly elevated fecal urobilinogen output. Because of these features, the possibility was recorded that the condition might terminate in pernicious anemia.

Clinical Course (fig. 8).—The patient was placed on a diet deficient in vitamin B complex and iron. During the first six days, 10 mg. of riboflavin was given daily by mouth. In two days there was moderate improvement in the lesions at the corners of the mouth; at the end of six days of treatment this improvement was much more noticeable, the lesion on the right being almost completely healed. One gram of ferrous sulfate was then given daily, the use of riboflavin being

16. Dameshek, W., and Valentine, E. H.: The Sternal Marrow in Pernicious Anemia, Arch. Path. **23**:159 (Feb.) 1937.

discontinued. After nine days the cheilosis was entirely healed, with slight scar formation. During this time there had been practically no change in the blood. The patient was discharged from the hospital on Aug. 27, 1940 and was followed in the blood clinic of the Boston Dispensary.

Continuing to take iron and a full diet including meat three to four times weekly, the patient had gained 7½ pounds (3.4 Kg.) by Oct. 14, 1940 and felt much stronger. Examination of the blood showed the hemoglobin concentration to be 75 per cent, and the red cell count 4,060,000. A seborrheic dermatitis appeared over the malar eminences, and riboflavin (10 mg. daily by mouth) was again given. Despite this medicament, the cheilosis reappeared by the next visit, November 15, and the tongue was still red and shiny. A daily dose of 0.7 Gm. of ferrous sulfate was continued, and nine yeast concentrate tablets daily were

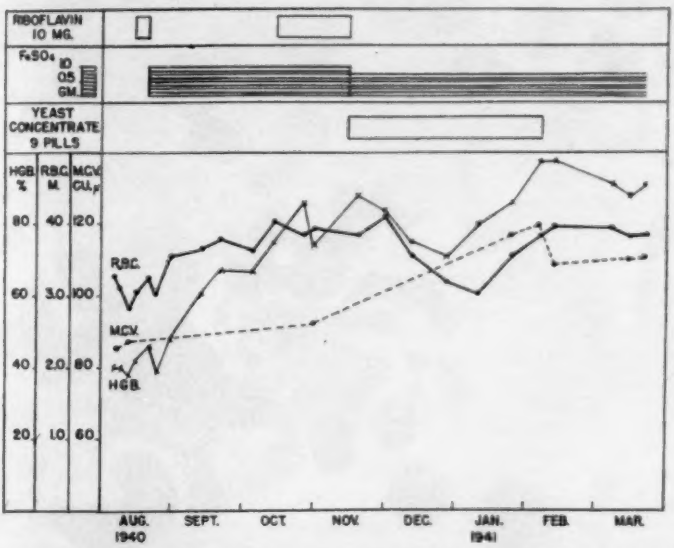

Fig. 8 (case 2).—Hematologic course. Note the relatively low hemoglobin concentration between August and October and the hyperchromia from approximately December to January, with rising mean corpuscular volume (*M.C.V.*).

substituted for the riboflavin. The cheilosis varied in intensity under this regimen, and the glossitis persisted. In November 1940 it was noted that the slight degree of anemia which was present was somewhat hyperchromic, and by Jan. 10, 1941 the hemoglobin concentration was 86 per cent, the red cell count 3,540,000, the hematocrit reading 42 per cent and the mean corpuscular volume 120 cubic microns. The cheilosis had become worse, despite iron, yeast and a full diet. The blood and bone marrow were carefully restudied on Feb. 13, 1941. Examination of the blood yielded the following information: hemoglobin concentration 98 per cent, red cell count 3,830,000, white cell count 6,900, platelets 440,000, hematocrit reading 46 per cent and mean corpuscular volume 120 cubic microns. The smear revealed hyperchromia and macrocytosis (fig. 9*A*), the mean cell diameter being 8.2

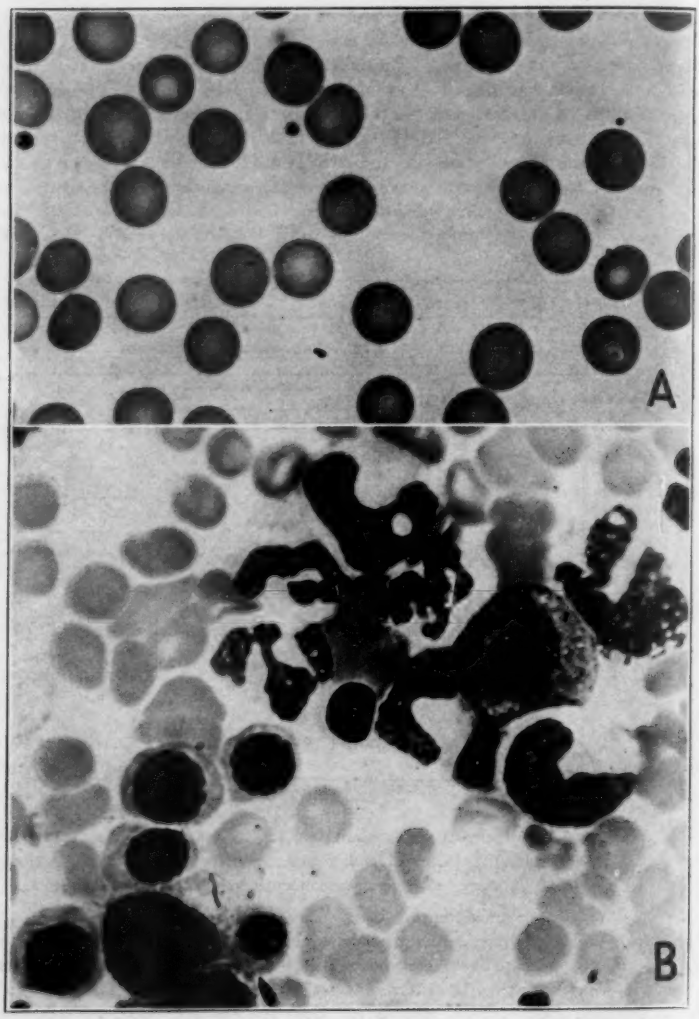

Fig. 9 (case 2).—*A*, photomicrographs of a blood smear (× 1,000) made Feb. 13, 1941 (compare with fig. 7 *A*). Note the well defined and uniform macrocytosis and the absence of hypochromia. The complete lack of microcytosis and of hypochromia was probably due to iron therapy. *B*, photomicrograph of bone marrow smear (× 1,000) made Feb. 13, 1941. Note the "giant" bizarre metamyelocytes and the megaloblasts, which are better hemoglobinized than those shown in figure 7 *B*.

microns (fig. 7 *II*). Differential count of smears from the sternal marrow puncture was as follows:

Type of Cell	Percentage	Type of Cell	Percentage
Myeloblasts	4.8	Erythrogones	1.4
Myelocytes	6.0	Megaloblasts A	5.6
Metamyelocytes	9.2	Megaloblasts B	25.6
"Giant" metamyelocytes	18.2	Megaloblasts C	6.0
Mature granulocytes	14.8	Normoblasts A	0.0
Eosinophils	1.8	Normoblasts B	0.2
Histiocytes	1.6	Normablasts C	0.2
Lymphocytes	4.6		

The megaloblasts at this time had their full complement of cytoplasm (fig. 9 *B*). Gastroscopic examination was repeated, and the observer (Dr. Henry Lerner) noted: "The mucosa was normal throughout, except for an area near the lesser curvature where the light reflex was considerably mottled and the mucous membrane was reddish green."

The patient has no neurologic manifestations and at present shows subsiding cheilosis, mild glossitis, mild hyperchromic anemia with macrocytosis and a bone marrow picture characteristic of a "liver extract" deficiency state. She was placed on a meat-free diet on which she relapsed. She has again been given large daily amounts of meat without liver or kidney. A reticulocyte and erythrocyte response and a great improvement in symptoms indicate a large element of "exogenous" pernicious anemia.

Comment on Case 2.—From the patient's history and the fact that iron was given in childhood and adolescence, it is probable that chronic iron deficiency has been present for many years. In adolescence, "chlorosis" might well have been diagnosed. As probable causes for the iron deficiency, one may list the long inadequate diet, the four pregnancies in rapid succession and a possible constitutional atrophy of the gastric mucosa, with achlorhydria. When first studied by us, the anemia was hypochromic, and the diagnosis of so-called "primary" hypochromic anemia was made because of the appearance of the tongue, the cheilosis, the complete achlorhydria and the absence of bleeding. However, because of a few atypical features—the normal mean corpuscular volume, the presence of some macrocytes, the peculiar appearance of the bone marrow, with bizarre giant metamyelocytes and hemoglobin-deficient megaloblasts, and the slightly increased hemolytic index—the possibility was suspected that this case might be an instance of transition from an iron deficiency state to one of "liver extract" deficiency (pernicious anemia). This possibility eventuated when iron was given in adequate dosage; as a result, the low color index disappeared and was finally replaced by hyperchromia and outspoken macrocytosis.

This case differs from the first one in that it is probable that the two deficiencies—iron and liver extract—were present simultaneously. The administration of iron in this instance did more than relieve a condition of iron deficiency; it "unmasked" a hidden or latent "liver extract" deficiency. The latter deficiency appears relatively mild in view of the almost normal erythrocyte count, the lack of neurologic involvement and the initial and well marked hypochromic character of the anemia. That a "mixed" deficiency is present in other cases of pernicious anemia is not unlikely. Usually, however, the deficiency in iron is slight and is "unmasked" when, following therapy with liver extract, the color index becomes low. Why there is not an outspoken iron deficiency as well in most cases of pernicious anemia is rather difficult to explain, since with an atrophic gastric

mucosa not only is protein digestion interfered with but iron digestion is impaired. It is possible that if one first treated patients with pernicious anemia with large doses of iron and observed the responses, a number of instances of mild iron deficiency would be uncovered. In any event, the existence of a mild pernicious anemia "hiding behind the back" of extreme hypochromic anemia is unusual. The occurrence of such an event makes one suspect that in other cases of primary, or idiopathic, hypochromic anemia, if observation was intensive enough and continued for sufficient lengths of time, the development of macrocytic, hyperchromic anemia of "liver extract" deficiency would be noted.

Relationships of Primary Hypochromic Anemia and Pernicious Anemia.—Castle and his co-workers [17] have shown that the normal gastric juice contains a ferment other than pepsin or rennin, designated as the intrinsic factor, which in the presence of proteins and perhaps the vitamin B complex (extrinsic factor) produces a substance, known as the hemopoietic principle, capable of inducing a remission in patients with pernicious anemia. In a case of typical addisonian pernicious anemia there is an insufficient amount [18] of this ferment. Castle, Heath and Strauss [1] further supported their theory with the demonstration of the presence of the intrinsic factor in cases of achlorhydria without anemia. Singer [19] and Hartfall and Witts [20] also found the intrinsic factor present in the gastric juice in cases of simple achlorhydric anemia (idiopathic hypochromic anemia).

Meulengracht [21] demonstrated that in the pig the intrinsic factor of Castle is produced in the pyloric region of the stomach and in the first portion of the duodenum. The submucous glands of the duodenum are similar histologically to the pyloric glands, and Meulengracht spoke of

17. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: I. The Effect of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, Am. J. M. Sc. **178**:748, 1929. Castle, W. B., and Townsend, W. C.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, ibid. **178**:764, 1929. Castle, W. B.; Townsend, W. C., and Heath, C. W.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: III. The Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding, ibid. **180**:305, 1930.

18. Goldhamer, S. M.: The Gastric Juice in Patients with Pernicious Anemia in Induced Remission, Am. J. M. Sc. **193**:23, 1937.

19. Singer, K.: Achylie und Anämie, Klin. Wchnschr. **11**:1459, 1932.

20. Hartfall, S. J., and Witts, L. J.: Intrinsic Factor of Castle in Simple Achlorhydric Anemia, Guy's Hosp. Rep. **83**:24, 1933.

21. Meulengracht, E.: The Glands of the Stomach in Relation to Pernicious Anemia, with Special Reference to the Glands in the Pyloric Region, Proc. Roy. Soc. Med. **28**:841, 1935.

them altogether as the "pyloric gland organ." From this evidence it has been assumed that this similarity exists in man also and that in pernicious anemia there is a diffuse atrophic lesion of the stomach also involving the duodenum, which would account for the lack of intrinsic factor in the gastric juice of patients with such disease. Should the atrophic process begin in the proximal half of the stomach, where hydrochloric acid and pepsin are secreted, and then later involve the pylorus and duodenum, as suggested by Hurst,[22] a simple explanation would exist for the cases in which primary hypochromic anemia precedes pernicious anemia. A predisposing tendency to atrophy of the stomach, with or without atrophy of the pyloric gland organ, could account for the familial relationship often seen in cases of simple achlorhydria, idiopathic hypochromic anemia and pernicious anemia. In cases of simple achlorhydria a combination of such factors as prolonged iron-poor diet, faulty intestinal absorption and diarrhea, with or without chronic hemorrhage, might finally result in the condition known as "primary," or "idiopathic," hypochromic anemia. There is much clinical evidence in support of the etiologic importance of these various factors. The investigations of Mettier and Minot [23] have suggested that achlorhydria may interfere with the proper absorption or utilization of organic iron. Intestinal malabsorption has also been shown to exist in cases of achlorhydric anemia.[24]

Magnus and Ungley [25] in 7 cases and Meulengracht [26] in 8 cases of typical pernicious anemia found a characteristic lesion of the stomach, which was localized to the fundic portion of the stomach and did not affect the pyloric gland organ. Since the glands of the fundus produce chiefly hydrochloric acid, there is a morbid histologic basis for the achlorhydria in pernicious anemia but not for the absence of the intrinsic factor—if one assumes that the latter is produced in the pars pylorus. Magnus and Ungley suggested that the pathologic mechanism in cases of pernicious anemia may be similar to that involving the islets of

22. Hurst, A.: Observation and Experiment and Physiology of the Stomach, Brit. M. J. **2**:183, 1937.

23. Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia, Am. J. M. Sc. **181**:25, 1931.

24. Singer, K., and Wechsler, L.: Klinische Bedeutung und Entstehungsmechanismus des Symptoms: Agalaktosurie, Wien. klin. Wchnschr. **47**:77, 1934. Heath, C. W., and Fullerton, H. W.: The Rate of Absorption of Iodide and Glycine from the Gastro-Intestinal Tract in Normal Persons and in Disease Conditions, J. Clin. Investigation **14**:475, 1935.

25. Magnus, H. A., and Ungley, C. C.: The Gastric Lesion in Pernicious Anemia, Lancet **1**:420, 1938.

26. Meulengracht, E.: Histologic Investigation into the Pyloric Gland Organ in Pernicious Anemia, Am. J. M. Sc. **197**:201, 1939.

Langerhans in cases of diabetes, in which the lesion is either functional or of an organic type not demonstrable by the histologic technics now available. Meulengracht suggested that the pyloric gland organ may be subject to the influence of a gastric hormone elaborated in the atrophic fundus.

The evidence gained from the literature seems to indicate that some persons possess a constitutional predisposition to gastric achlorhydria, which is often familial. This state need not be associated with anemia or other symptoms. During the stage of simple achlorhydria, hypochromic anemia may result, especially if another factor, such as dysphagia, inadequate diet, intestinal malabsorption or hemorrhage, is present. Occasionally, by an unknown mechanism, the intrinsic factor of Castle may become seriously diminished, with the result that pernicious anemia develops. In our first case, there seems to have been constitutional atrophic gastritis with gastric achlorhydria. During a period of emotion, dysphagia appeared, and because of this difficulty a diet greatly deficient in iron-containing foods was taken. As the result of these various factors, a chronic iron-deficiency state appeared. A few years later, probably as the result of either functional or organic involvement of the pyloric gland organ, the intrinsic factor probably became greatly diminished with the result that pernicious anemia developed.

In our second case, "primary" hypochromic anemia and pernicious anemia were apparently coexistent, although the iron deficiency state was sufficiently outstanding to result in the diagnosis of the first entity. When iron was given, the anemia became macrocytic and the underlying pernicious anemia was "unmasked."

SUMMARY

Two cases of "primary" hypochromic anemia which terminated in pernicious anemia are reported. In the first case, in which the hyperchromic anemia was associated with the Plummer-Vinson syndrome, pernicious anemia developed after several years of observation. In the second case, the administration of iron apparently "unmasked" underlying and coexistent pernicious anemia. The possible mechanisms and the theoretic implications of these transitions are discussed.

THE NATURAL HISTORY OF BRONCHIECTASIS

A CLINICAL, ROENTGENOLOGIC AND PATHOLOGIC STUDY

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This study was made in an attempt to trace the natural development of bronchiectasis in a series of cases.

An examination of the voluminous literature yielded much that was helpful, but also much that appeared to be contradictory and confusing. It was felt, therefore, that a fresh start must be made and any conclusions must be based on the continued observation of a number of actual cases. The literature was, therefore, referred to chiefly for the purpose of comparison and for amplification of those aspects which appeared to be inadequately covered by the evidence from the present series.

The subject was a large one, and the method of its treatment was seriously considered. The disadvantages of employing the "textbook" method were realized, but were regarded as capable of exaggeration. No other means of approach can compare with it for comprehensiveness, clarity and ease of reference.

The disease, therefore, was dealt with under the headings of pathogenesis, etiology, clinical features, roentgenologic aspects, classification and prognosis. Treatment was regarded as outside the scope of this article, but the indications as illustrated by this and other series of cases are mentioned in the text. A short section on anatomy and physiology is introduced as a useful preliminary to the study of the abnormal condition.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

Bronchial Tree.—The mode of branching of the bronchial tree has been a subject of controversy, and a dissection of a normal lung was therefore made. From this dissection it became clear that bronchial branching is monopodial as far as the finer bronchi, i. e., the smallest capable of gross dissection. Dichotomy then becomes the method of choice, and Willson [1] stated that this is followed as far as the alveolar ducts, except where it conflicts with the overriding law of the economy of space, which is rigidly observed.

This paper represents the substance of an essay accepted for the degree of Doctor of Medicine at the University of Durham, Durham, England.

1. Willson, H. G.: Am. J. Anat. **30**:267, 1922.

The various lobular areas which have been described as likely to form supernumerary lobes were readily recognized. With the exception of the lingular lobe, no instances of supernumerary lobes were confirmed at operation or autopsy in the present series, although such lobes are generally regarded as peculiarly liable to the development of bronchiectasis.

The normal bronchial structure is of the utmost importance in any study of abnormal bronchi, and a brief account of the salient points is therefore given.

The bronchi are to be regarded as tubes of muscular and elastic tissue, the "myo-elastic" tissue of Macklin,[2] which are enclosed in a sheath of collagen and elastica, stiffened by cartilaginous plates and lined by a contniuous sheet of epithelium. The arrangement of this "myo-elastic" tissue is most important. Internally, beneath the mucosa, is a layer of branched elastic fibers, which is succeeded by flat, branching muscular bundles, among which run numerous elastic fibers. The muscle is loosely packed, with angular spaces between the bundles, and is thus arranged in the form of a branching network. The elastic fibers run parallel to the muscle strands. Macklin described the arrangement as a "branched tubular net." This association of muscle and elastic tissue becomes even more intimate as the finer bronchial tubes are reached, and the tunica propria disappears as a separate layer. The muscle of the bronchi, although the direction of the fibers varies from point to point, is neither circular nor longitudinal, but rather oblique. Miller [3] used the term "geodesic network" suggested by Max Mason. It is of interest to note that the fuselage of the new Wellington bomber is constructed in a somewhat similar fashion.

Miller's description of the bronchial blood supply is classic and well known, and it is not proposed to do more than to point out how liable is the internal capillary network to hemorrhage in destructive lesions of the tubes.

There is general recognition of the fact that the bronchi play an important part in respiration and are not mere passive conducting channels. During inspiration the bronchial muscle relaxes, and, owing to the arrangement of the myoelastica, the tubes widen and elongate. Their narrowing and shortening again on expiration is due to active contraction of the muscular and natural recoil of the elastic tissue. Muscle and elastica act evenly and harmoniously together.[4] Ingals [5] and Jack-

2. Macklin, C. C.: Physiol. Rev. **9**:1, 1929.

3. Miller, W. S.: The Lung, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

4. Willson.[1] Macklin.[2]

5. Ingals, E. F.: Respiratory Movements of the Bronchial Tubes. J. A. M. A. **45**:1302 (Oct. 28) 1905.

son [6] observed these movements through the bronchoscope, and general agreement thus far appears to have been obtained. The work of Bullowa and Gottlieb [7] and of Hudson and Jarre [8] was also of importance in this connection.

Is this change in capacity, together with ciliary action, the whole story of bronchial function? Horvath [9] and von Schrotter [10] described a peristaltic movement of the bronchi, but little attention seems to have been paid to their views for some years. Bullowa and Gottlieb [7] and Reinberg [11] revived interest in the question. These workers observed waves of peristalsis 10 cm. in extent, when radiopaque material was

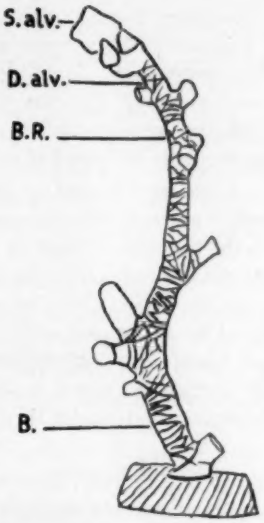

Fig. 1.—Model of a noncartilaginous bronchiole from a dog's lung, showing the muscular arrangement when the bronchiole is in a condition of full inspiration. *B.*, bronchiolus; *B. R.*, bronchiolus respiratorius; *D. alv.*, ductulus alveolaris; *S. alv.*, sacculus alveolaris (Miller [3]).

introduced into the bronchi. Reinberg made his observations on a patient with paralysis of the recurrent laryngeal nerve and described the phenomenon as "tracheal vomiting." These movements could be differen-

6. Jackson, C.: Bronchoscopy and Esophagoscopy, ed. 2, Philadelphia, W. B. Saunders Company, 1927; Tr. Am. Laryng. A. **40**:319, 1918.

7. Bullowa, J. G. M., and Gottlieb, C.: Am. J. M. Sc. **160**:98, 1920; Laryngoscope **32**:284, 1922.

8. Hudson, W. A., and Jarre, H. A.: Grace Hosp. Bull. **13**:15, 1929.

9. Horvath, A., cited by Reinberg.[11]

10. von Schrotter, cited by Reinberg.[11]

11. Reinberg, S. A.: Brit. J. Radiol. **30**:451, 1925.

tiated from transmitted impulses and were independent of coughing, which either hastens the centrifugal movement of material or "splashes it peripherally." Jackson was unable to confirm bronchial peristalsis, but probably the bronchoscope is not the best means of observing such a phenomenon. Ellis [12] pointed out that records from two fixed points in the same bronchial tube are required for proof that the evidence is at least strongly suggestive. Macklin summed up the evidence by saying that peristalsis is probably slight under normal conditions but plays the major part in the expulsion of secretions and foreign bodies.

The presence of abundant sensory nerve endings in the bronchial wall and the existence of Remak's ganglion show that an apparatus for peristaltic action exists. It appears that the bronchi have a passive role in inspiration, but that in expiration the active contraction of the myoelastic tissue plays an important part. In the expulsion of secretions and foreign material from the lung the ciliary action and probably bronchial peristalsis are together responsible for shepherding these substances to a point whence they may be expelled by coughing.

Air Sacs and Alveoli.—Little need be said on this subject. The chief, if not the only pertinent, feature of the alveolar arrangement is the relation of the air cells to the bronchi. This is in reality complex, but it is unnecessary to go into detail here. All intrapulmonary bronchi are completely surrounded by air cells. The bronchial system is thus strengthened and supported by a vast and most efficiently disposed air cushion, consisting of no fewer than 725,000,000 minute but inflated alveoli. It will be readily appreciated that a condition of atelectasis will deprive the tubes of this support and render them liable to dilatation.

PATHOGENESIS

ACQUIRED BRONCHIECTASIS

A discussion of the numerous theories is both unnecessary and likely to prove tedious, if not confusing. Ballon, Singer and Graham [13] recently studied the matter exhaustively, and reference to their monograph is suggested. All the possible causes of bronchiectasis which have been mentioned in the literature can, moreover, be grouped under two headings:

1. Defects in the bronchial wall.
2. The various stresses and strains to which the bronchial wall may be subjected.

Defects in the Bronchial Wall.—Acquired bronchial defects have been stated to be due to damage caused by infective processes or by

12. Ellis, M.: Lancet **1**:819, 1938.

13. Ballon, H.; Singer, J. J., and Graham, E. A.: J. Thoracic Surg. **1**:154, 1931.

inorganic substances, such as silica and poisonous gases. A contributory factor which has been emphasized by Ameuille and Lemoine [14] is interference with bronchial nutrition by vascular disease of the bronchi.

The extraordinary efficiency of the myoelastic tissue, which has already been described in some detail, indicates that serious weakening of the wall can be produced only by actual destructive changes, which must extend to the deeper layers. Minor localized areas of damage are, by themselves, insufficient to produce it, although extensive inflammatory changes short of destruction may interfere with bronchial function sufficiently to favor the maintenance of an infective process and to reduce bronchial elasticity.

The first step must, therefore, be to examine the available evidence as to the actual condition of the bronchial wall in bronchiectasis. It is preferable that this evidence should be based on the study of "living" lobes rather than of postmortem material, for obvious reasons, but the relatively recent expansion of the scope of lobectomy limits the possibilities of this method. The only pathologic studies of lobes removed at operation which I have been able to review are those made by Robinson [15] and Goodman,[16] the work of Sauerbruch [17] and the report on lobes studied at Brompton Hospital, given by Lander and Davidson [18] in their recent article.

Robinson examined 16 lobes excised by Janes from 10 patients. He found as the outstanding and most consistent observation a "chronic inflammatory condition of the bronchial walls with various degrees of damage up to complete destruction of the musculo-elastic tissue." He visualized early paresis of the muscle, due to infection, which leads to dilatation. At this stage, he stated, recovery may occur, but with persistent or more severe infection permanent damage results. This change, in its turn, favors further persistence of infection, and a vicious circle becomes established. He found no evidence of significant collapse or pleural adhesions in his patients.

Goodman was emphatic as to the pronounced changes in the bronchi and peribronchial tissue, although he did not give details. He said:

> The pathological features of all these cases was very impressive. The lobes in all cases were markedly adherent to surrounding structures in the chest. There was considerable induration throughout the lobe with very little crepitation noticeable. On section they all showed markedly dilated and thick-walled bronchi. The tissue around the bronchi appeared hepatized, hemorrhagic and in some cases undergoing suppuration.

He also mentioned the purplish blue to dark slate color of the lobes.

14. Ameuille, P., and Lemoine, J. M.: Presse méd. **43**:873, 1935.
15. Robinson, W. L.: Brit. J. Surg. **21**:302, 1933.
16. Goodman, H. I.: Am. J. Surg. **26**:543, 1934.
17. Sauerbruch, F.: Chirurgie der Brustorgane, Berlin, Julius Springer, 1929, vol. 1, pt. 1, p. 869.
18. Lander, F. P. L., and Davidson, M.: Brit. J. Radiol. **11**:65, 1938.

Sauerbruch desecribed two types of bronchiectasis, "congenital" and "inflammatory." The "congenital" type will be considered at the end of this section, but it may be stated here that he expressed the opinion that it is to be found in all children in whom bronchiectasis is confined

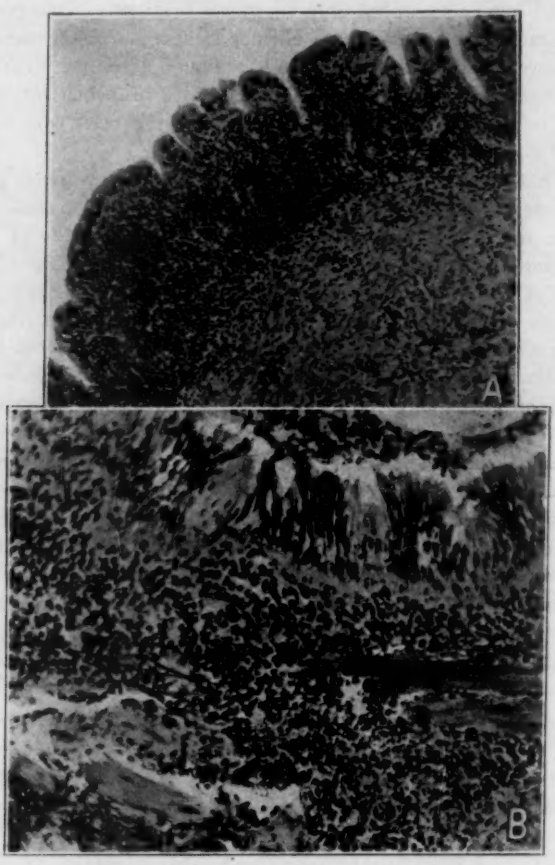

Fig. 2.—*A*, "inflammatory infiltration of the subepithelial layer"; *B*, "degenerative changes in muscle fibers and some splitting of the elastic lamellae are shown." [15]

to one lobe and that the lobe thus affected is atelectatic. Pleural adhesions are absent. In the "inflammatory" type the position and sequence of the layers in the bronchial wall are clearly discernible, but the muscle and elastic fibers are split up. There are metaplasia of the epithelium

and resorption, and even calcification, of the cartilage. Granulations "spring up" in the diseased areas (and may lead to hemorrhage which is evident clinically). If obstruction is present even the neighboring pulmonary tissue may be destroyed. Sauerbruch remarked that in this type more than one lobe is usually affected, and did not mention atelectasis as a feature.

Evidence of infection was clear in both these accounts, but it is rather difficult to explain the slight degree of bronchial damage which Sauerbruch seemed to indicate is associated with destruction of the surrounding pulmonary tissue. Furthermore, the granulations which "spring up" clearly indicate a destructive change.

Lander and Davidson were more emphatic as to the minimal bronchial damage which may be observed. They stated that examination of 140 lobes removed from patients at the Brompton Hospital showed that infection was negligible in those specimens. "A histological study . . . shows not only an intact mucous membrane, very often ciliated, . . . but also the presence of all the normal layers of the bronchial wall." The only exceptions to this observation were found in sections taken through saccules, which showed epithelial lining and fibrous tissue only and were always peripherally situated. The authors expressed the opinion that they were "probably caused by the extreme dilatation of minute bronchi and bronchioles, which normally contain no glands, no cartilage, and a minimal amount of muscle." Pleural adhesions were exceptional in their specimens, they said, while the lobes were collapsed to a greater or lesser extent. There was no mention of any bronchial destruction, such as Robinson described, or of any granulations, such as Sauerbruch mentioned. Such a conflict of experience is disconcerting and is difficult to explain as coincidental.

A study of the pathologic features of the present series, therefore, seemed the most obvious step, and the following account is a summary of the results of this study.

Lobectomy was performed in 35 cases. Excised lobes from patients in 28 of these cases, comprising 35 specimens, were available for study.

A. Macroscopic Appearance: Comment will be limited to an account of the condition of the pleura and of the general appearance of the parenchyma.

The condition of the pleura is of interest in view of the statements as to the prevalence of a normal pleura in bronchiectatic lobes. It was found easy to divide the specimens into two groups: those in which gross thickening was associated with the presence of stout tags representing divided adhesions, and those in which changes were moderate or absent.

The pleura was much thickened in 25 specimens, while pleural changes were minor in only 10 specimens. These figures do not lend support to the view that pleural changes are usually slight or absent.

The general appearance of the parenchyma and the actual size of the excised lobe or lung were studied because sections of a whole lobe were available in only a minority of the cases. Small sections gave a less satisfactory idea of the condition of the lobe as a whole, and the appearance to the naked eye was helpful on this account.

The specimens were divided into three groups on a second basis: those in which collapse was really extensive, or apparently complete; those in which collapse was patchy or local, and those in which collapse appeared to be negligible. In the tabulation which follows, these groups are shown in relation to the size of the lobe and the presence of parenchymal scarring and emphysema, which was regarded as probably compensatory.

Collapse	No. of Specimens	Size of Lobe	Scarring of Parenchyma	Emphysema
Extensive	22	All shrunken	10	6
Local or patchy	9	All normal	4	8
Negligible	4	All normal	1	4

The high proportion of specimens showing extensive or apparently complete collapse is noteworthy, as is the fact that in all of these the lobe was definitely shrunken. Apparent parenchymal scarring was noted in more than one third of the specimens. No further comment seems necessary.

B. Microscopic Examination: Histologic sections of 31 specimens were available for study. For a minority of these specimens sections of the whole lobe or the whole lung were available, and for the others there were smaller sections only.

Particular attention was paid to the condition of the bronchial wall and to any evidence of inflammation or damage which it might present. In addition, the parenchyma of the lung was studied, and the state of the vessels, the lymphoid tissue and the bronchial mucous glands was noted. Conditions varied in different specimens and in different parts of the same specimen.

In the majority, however, more or less severe bronchial destruction was evident, and all showed well marked inflammatory changes.

The condition of the parenchyma varied, also, but the preponderance of extensive pulmonary collapse, noted in the foregoing account of the macroscopic appearance, was confirmed. Other parenchymal changes were patchy or confluent bronchopneumonic consolidation and emphysema. Emphysema was noted in all specimens and varied from small patches to extensive areas, even in specimens in which collapse appeared complete on gross inspection. This last observation was interesting and rather unexpected, as little or no mention of emphysematous areas was

made in the literature and from accounts of "atelectasis" one gained the impression that collapse is complete.

Endarteritis was noted in all specimens, and in many it was gross and widespread. Lymphoid hyperplasia was conspicuous throughout, and in most specimens a pronounced increase in the number of bronchial

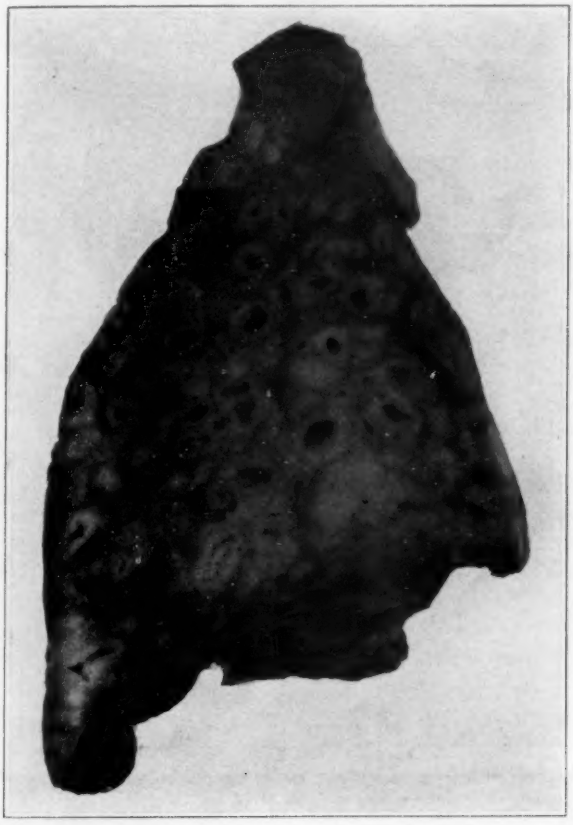

Fig. 3.—Specimen from lobectomy; actual size. The bronchiectasis was of the bronchopneumonic type. The patient was a child of 13.

mucous glands was noted. The latter changes were regarded as important, because they are so typically associated with inflammation of long standing.

For purposes of more detailed description, it was found convenient to divide the specimens into two groups on a third basis.

1. Specimens in which pulmonary collapse was extensive, the "atelectatic" group: This group comprised 21 specimens.

The bronchial lining was usually complete, although in places a break in continuity was observed. The lining was composed of columnar and squamous epithelium, and in most bronchi the transition from the one to the other was seen. Cilia were rarely observed. Certain of the

Fig. 4.—Specimen from lobectomy; actual size. The bronchiectasis was of the atelectatic type. The patient was a child of 12.

bronchi were lined completely by columnar or by squamous epithelium, as the case might be, but these were in the minority. A feature of the squamous epithelium was its tendency to be heaped up into layers.

The lumens of the bronchi were frequently stellate in cross section, giving an appearance which has been recorded in the literature and has been variously interpreted. Opie expressed the opinion that it was due to splitting of the bronchial wall in certain places, with subsequent sealing by scar tissue. Bronchial inflammation was easily apparent in all specimens, but wide variations in the condition of the wall were seen.

All grades of inflammation were observed, from the presence of a complete muscle layer and absence of scar tissue to more or less complete replacement of the bronchial structure by organizing granulation tissue showing evidence of scarring.

In some specimens the majority of bronchi were relatively normal, though inflamed, whereas in others most of them were extensively damaged. Some bronchi occupied a roughly intermediate position. In general, the cartilage did not apppear to be grossly affected.

Eleven specimens (52.5 per cent) showed evidence of severe destruction. Eight specimens (38.0 per cent) showed evidence of more moderate destruction and 2 specimens (9.5 per cent) evidence of slighter damage. It is clear that bronchial destruction was, on the whole, a prominent feature in these specimens.

Along with bronchial inflammation were noted changes in the vessels in the form of endarteritis, hyperplasia of the lymphoid tissue and increase in the number of mucous glands.

The granulation tissue, which in cases of severe damage replaced the normal bronchial structure, was typical and highly vascular, with the new vessels directed toward the surface and with fibers of young scar tissue running through it like a skein.

The parenchyma was, as has been indicated, extensively collapsed, but in no case was this collapse complete and in a few was far from being so. In sections of a whole lobe the emphysema was usually seen as strips of varying width occupying the periphery of the section, but in 1 case the central portion was emphysematous and the remainder collapsed. In the case of 1 specimen doubt was felt as to its proper inclusion in this group, owing to the degree and extent of emphysema. It was considered, however, that the extreme distention of the emphysematous area exaggerated its true extent, considered in terms of lung area.

Patches of emphysema were noted, also, to be scattered here and there through the central part of the sections.

It is thus evident that collapse is far from complete even in lobes which are solid and shrunken and which are dense enough to produce a typical "atelectatic" shadow in a roentgenogram.

Parenchymal scarring was evident in varying degree in 10 specimens, but was mainly peribronchial. Patches of bronchopneumonia were occasionally seen, but were inconspicuous.

2. Specimens in which collapse was patchy or negligible, the "bronchopneumonic" group: This group comprised 10 specimens, 8 (80 per cent) of which showed evidence of severe destruction and 2 (20 per cent) evidence of moderate destruction.

In all 10 specimens scarring of the parenchyma was evident. The number was small, but there was a suggestion of rather more severe bronchial damage in this group, which was called the bronchopneumonic group on account of the prominence of patchy or confluent broncho-

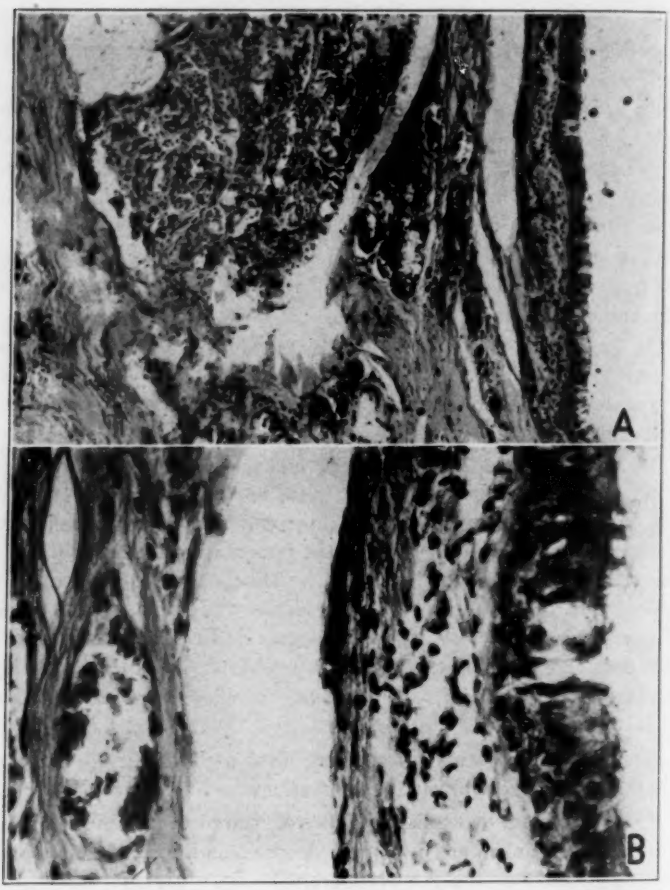

Fig. 5.—*A*, wall of a normal bronchus; 2/3 power lens. Note the normal arrangement of epithelium and muscle tissue and the presence of mucous glands and vessels. *B*, a portion of the wall more highly magnified to show its structure in detail; 1/6 power lens.

pneumonic consolidation and of parenchymatous scarring and the relative absence of collapse.

The histologic appearances of the bronchi presented no striking qualitative differences from those already described in the atelectatic group. Endarteritis and lymphoid hyperplasia were conspicuous. The parenchymal changes differed considerably.

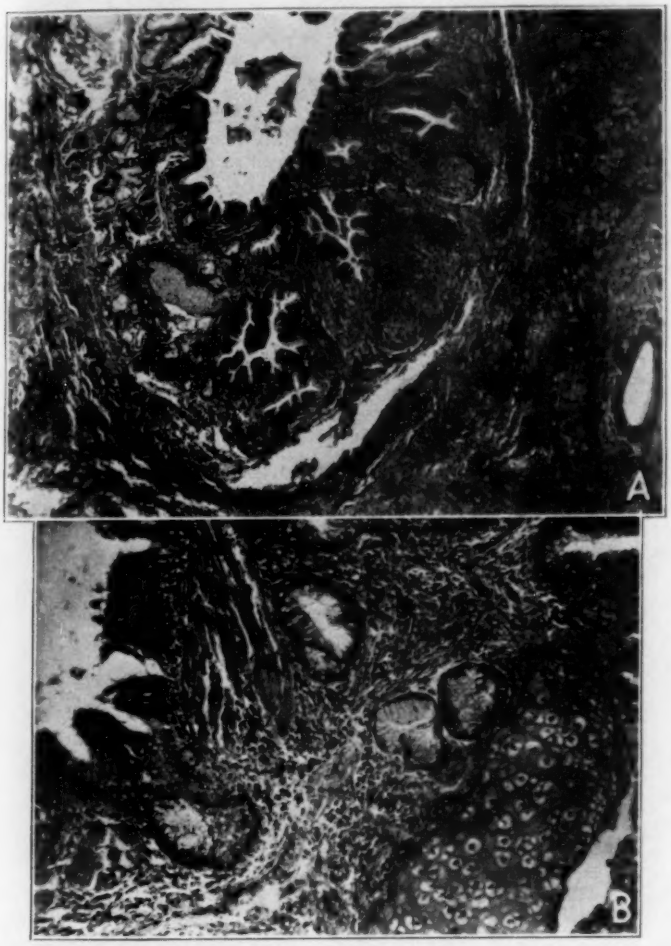

Fig. 6.—Atelectatic bronchiectasis. *A*, a section through a portion of diseased lung shows collapse of the parenchyma, hyperplasia of lymphoid tissue and excess development of mucous glands; 2d power lens. *B*, a portion of the section is more highly magnified to show the wall of the chief bronchus in detail. Note that the muscle is in a fairly good state of preservation but that inflammation is evident. Granulations, containing new blood vessels and a few strands of scar tissue, are present. 2/3 power lens.

Patches of collapse were noted in some sections, but in none were they a prominent feature. For the most part, patchy or confluent consolidation, peribronchial in distribution, alternated with areas of

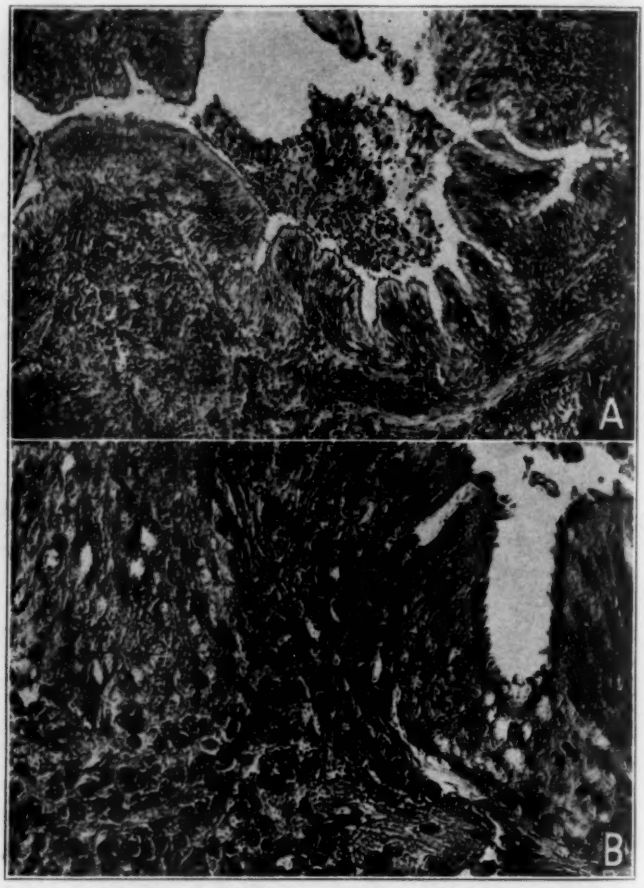

Fig. 7.—In *A*, from another case of atelectatic bronchiectasis, the bronchial damage is much more extensive. The wall is composed chiefly of highly vascular granulation tissue. Note the numerous young blood vessels. There is definite evidence of organization; "skeins" of scar tissue are present; muscle is scanty. 2/3 power lens. In *B*, a more highly magnified portion of the bronchial wall, a muscle bundle is visible, but is undergoing degenerative change. Granulation tissue is obvious. There is a break in the continuity of the columnar epithelium at one point, but multiplication of the basal cells to repair the break is taking place. It is noteworthy that ciliated columnar epithelium lines such an abnormal bronchus. Obviously, this is the result of a regenerative process. 1/6 power lens.

emphysematous or air-containing pulmonary tissue, and evidence of destructive pulmonary changes was noted in a few areas.

Comment: It appeared from this pathologic study that bronchiectatic lobes removed from living patients commonly show pronounced changes.

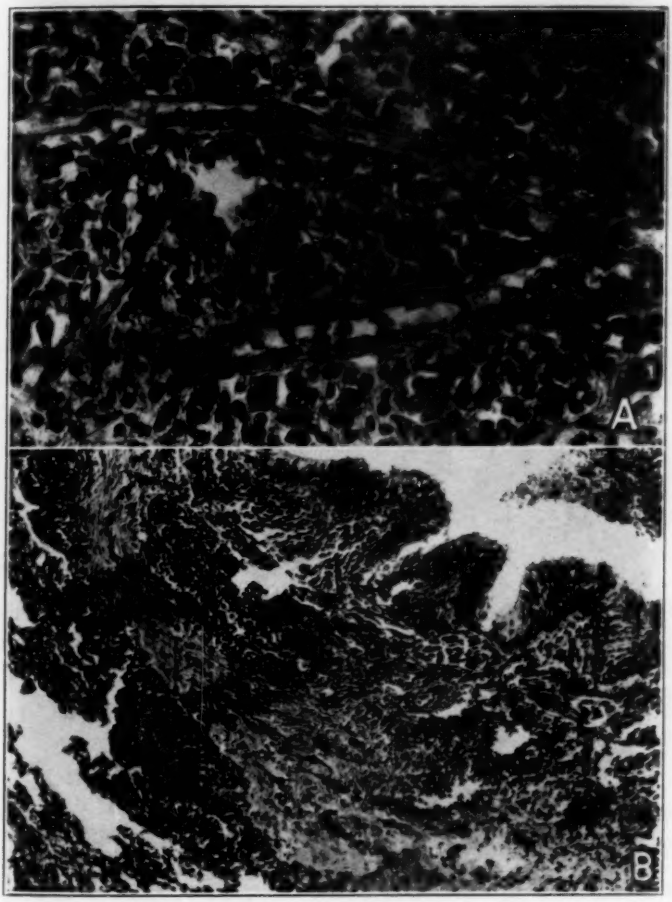

Fig. 8.—*A*, granulation tissue and formation of new vessels in the bronchial wall; 1/6 power lens. *B*, inflammation of the bronchial wall and peribronchial scarring. The bronchial muscle is well preserved. 2/3 power lens.

Not only was considerable inflammation a prominent feature, but actual destruction of the bronchial wall was frequently found. Those other changes which are to be expected in association with chronic

bronchial inflammation of any severity were observed. These were endarteritis, lymphoid hyperplasia and hypertrophy of mucous glands.

Brock [19] recently emphasized the pronounced changes in lymphoid tissue seen at operation. He said that "the importance of the lymph glands . . . is constantly forced upon one in lobectomy for bronchiectasis

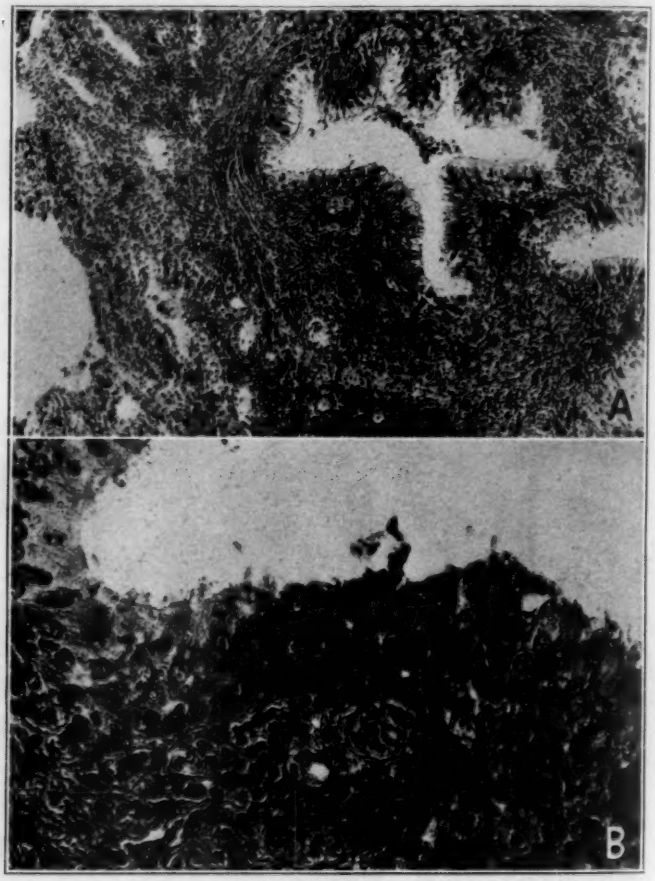

Fig. 9.—Bronchopneumonic bronchiectasis. *A*, transition from columnar to squamous epithelium over a portion of the bronchial wall and the granulation tissue, which comprises most of the bronchial wall; 2/3 power lens. *B*, a portion of the bronchus more highly magnified to show in detail the transition from columnar to squamous epithelium and the nature of the bronchial wall; 1/6 power lens.

19. Brock, R. C.: Lancet **2**:1103. 1938.

when they are almost always found large and inflamed and obtrude themselves markedly when the fissure is being cleared."

Extensive collapse of the parenchyma was frequent in the excised lobes, though it was never really complete. These atelectatic lobes were

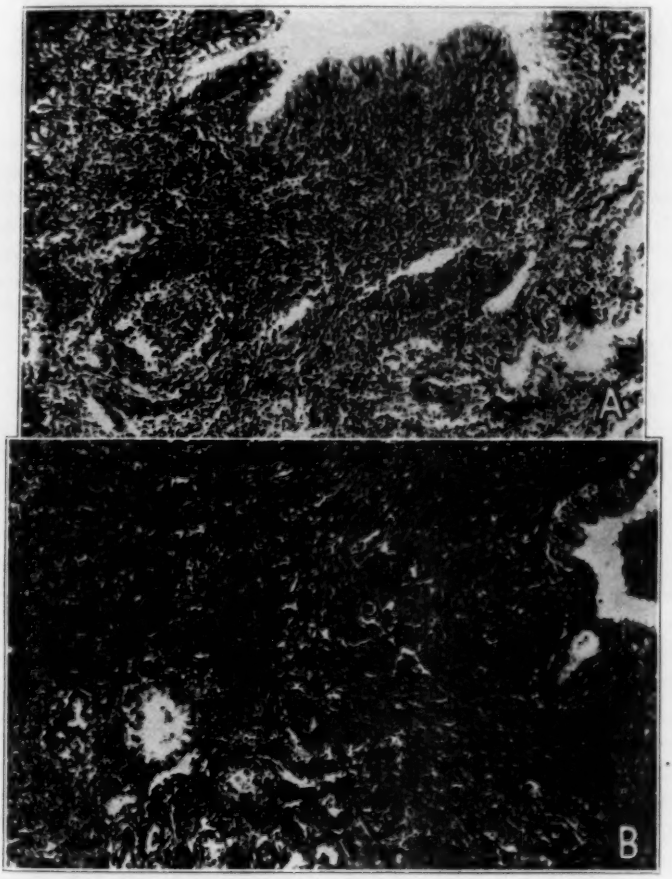

Fig. 10.—Bronchopneumonic bronchiectasis. *A*, the columnar epithelium which lines the bronchus has one break in its continuity; it is replaced by squamous epithelium. Vascular granulation tissue, in which there are a few "skeins" of scar tissue, is visible. No muscle tissue can be observed. 2/3 power lens. *B*, a portion of the section in close proximity to the bronchus is magnified more highly to show an area of bronchopneumonic consolidation with destruction. 2/3 power lens.

by no means free of inflammation and bronchial destruction, however—quite the contrary.

That these changes were the direct result of infective processes was indicated by the constant replacement of destroyed elements by granulation tissue, which showed definite evidence of organization into scar tissue in the usual way.

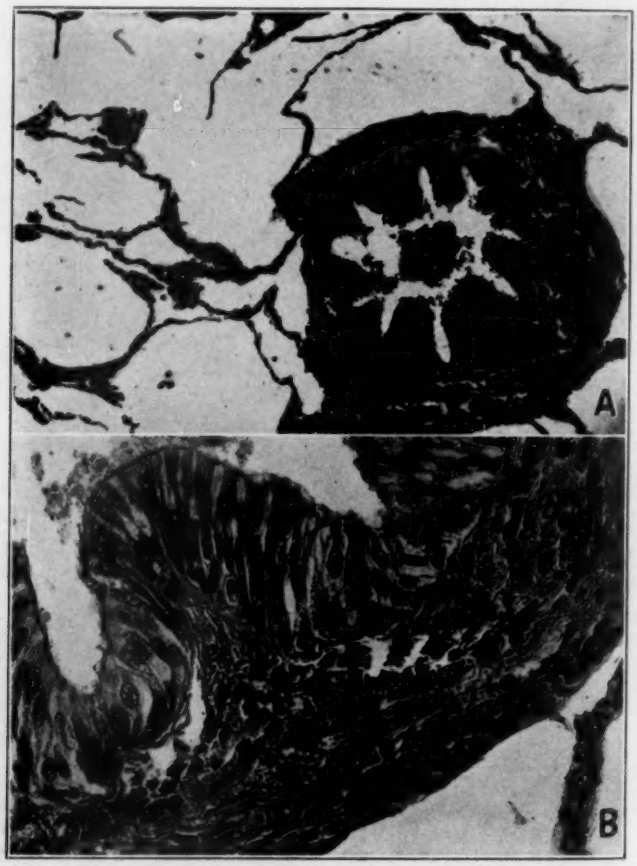

Fig. 11.—Bronchopneumonic bronchiectasis. *A*, damaged bronchus, in an emphysematous area, with debris in its lumen; 2/3 power lens. *B*, a portion of the section more highly magnified to show the bronchial wall in detail; 1/6 power lens. There is evidence of inflammation and the formation of scar tissue. No muscle is visible here, although a few strands were noted elsewhere in the wall of this bronchus.

The condition of the pleura must also be considered. The fact that gross pleural thickening was noted in 25 of 35 specimens suggests that pleural adhesions were a common feature of the excised lobes. As a

check on this, the records in 50 cases in which the patients were operated on by Mason have been studied. These cases were selected at random. It was found that in no less than 21 the diseased lobe was densely adherent, requiring the use of scissors for its removal. In only 7 cases was the pleura absolutely free.

These figures cannot, of course, be accepted as an indication of the incidence of pleural adhesions in cases of bronchiectasis in general, but they certainly show that adhesions are not uncommon.

These observations are directly at variance with those of Lander and Davidson, who reported that a normal bronchial wall, with negligible infection, and a free pleura were almost constantly found. The great frequency of collapse in bronchiectatic lobes in our series, a feature which they also stressed, was, however, in accordance with their experience.

Robinson's description of the bronchial wall agrees closely, however, with the appearance in this series of excised lobes, and Sauerbruch's account of granulations "springing up" in the diseased areas suggests that he observed similar changes.

Opie and associates,[20] Erb [21] and McNeil, MacGregor and Alexander,[22] whose studies are all comparatively recent, noted changes very like those recorded here, although rather more advanced. Excavation of the lung, for example, was a prominent feature in some of their cases, whereas it was only occasionally seen in the excised lobes in our series, and then in the bronchopneumonic group. They worked with postmortem material, which is admittedly less satisfactory than "living" specimens, but their reports, being those of eminent pathologists, cannot be disregarded completely on this account. The photomicrographs published by Erb and by Opie and his associates are almost identical with those reproduced in this essay, as comparison will prove. MacCallum [23] also described pronounced bronchial damage.

The available evidence on the condition of the bronchial wall in bronchiectasis indicates, therefore, that the wall is frequently the subject of an infective process, which not uncommonly progresses to actual and possibly extensive, destruction. There is thus strong support for the view that definite weakening of the bronchi exists in many cases.

20. Opie, E. L.; Blake, F. G.; Small, J. C., and Rivers, T. M.: Epidemic Respiratory Disease, St. Louis, C. V. Mosby Company, 1921.

21. Erb, I. H.: Pathology of Bronchiectasis, Arch. Path. **15**:357 (March) 1933.

22. McNeil, C.; MacGregor, A., and Alexander, A.: Arch. Dis. Childhood **4**:170, 1929.

23. MacCallum, W. G.: Textbook of Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 410.

In yet others there is every reason to suppose that the important function of the bronchi in the removal of the products of infection and foreign material, which was described in the foregoing section on the

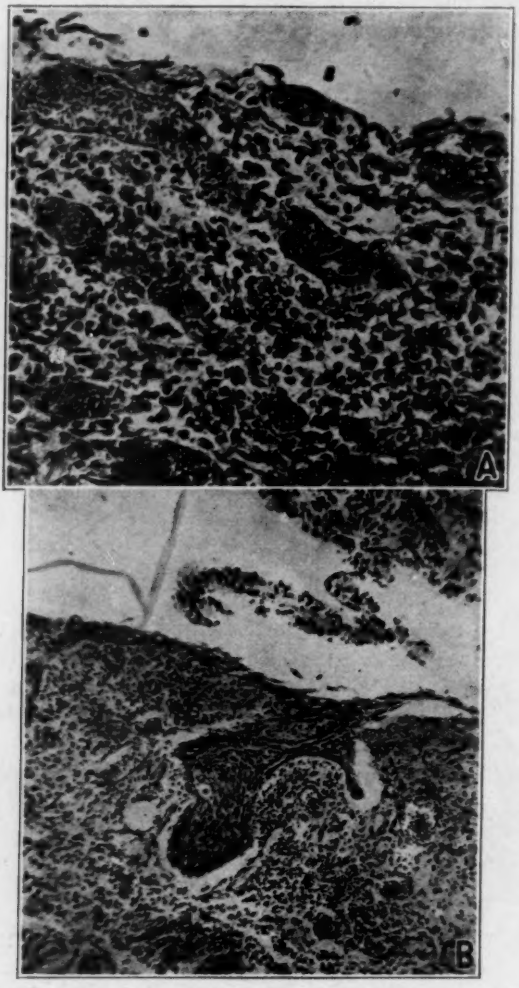

Fig. 12.—"*A*, wall of bronchus lined by granulation tissue (case 8; duration six and one-half weeks); × 240. Note absence of muscle and elastic fibers. *B*, granulation tissue of bronchial wall becoming lined by squamous epithelium (same case); × 120." [21]

anatomy and physiology, is seriously interfered with, thus favoring persistence and extension of destructive processes.

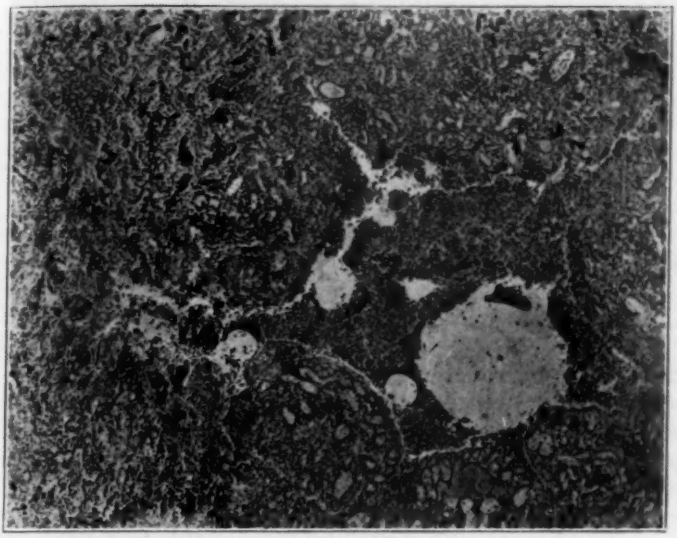

Fig. 13.—"Acute bronchiectasis with fissures extending through bronchial wall, which is marked by great engorgement of blood vessels: at one point a fissure has penetrated deep into the alveolar tissue and formed a small cavity containing purulent exudate and surrounded by fibrinous pneumonia." [20]

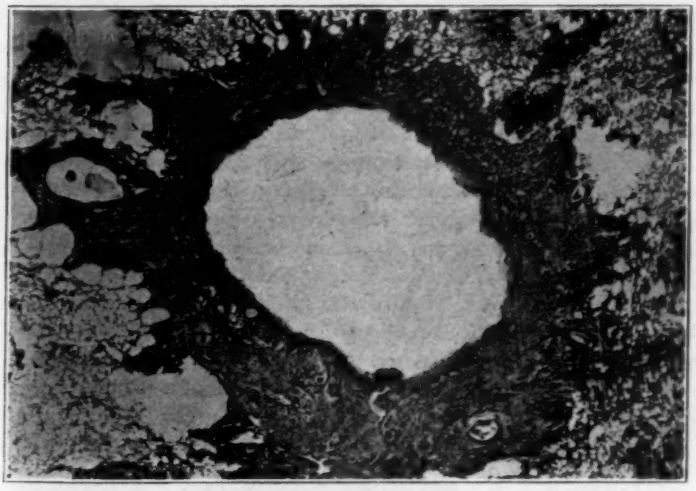

Fig. 14.—"Unresolved pneumonia with bronchiectasis, showing new formation of fibrous tissue about a greatly dilated bronchus, of which the epithelial lining has been lost." [20]

Strains and Stresses to Which the Wall of the Bronchi May Be Subjected.—The intrabronchial pressure was given by Hedblom [24] as 10 to 20 cm. of water. It is common knowledge that the normal bronchial wall, when supported by aerated lung tissue, withstands this pressure, although it is conceivable that a weakened bronchus might give way, as he suggested.

This pressure may be increased in several ways. Laennec [25] advanced the view, which has been repeated frequently, that the pressure of retained bronchial secretions might cause bronchial dilatation. However, this force cannot be measured, and the theory is not susceptible of proof or disproof. It remains as a possibility that a greatly weakened bronchus might yield to such pressure.

A much more certain, and probably more frequent, cause of raised intrabronchial pressure is collapse of the lung, which has been proved to act in this way. Airlessness of the neighboring parenchyma removes the strong "cushioned" support given normally to the bronchi by aerated lung tissue, thus producing a real intrabronchial pressure greatly above normal.

Lander and Davidson [18] showed that the mean negative pleural pressure in cases of pulmonary collapse may rise to 27 cm. of water. This means that an atmospheric pressure of 37 to 47 cm. is acting on the bronchi, and these authors further showed that this pressure does dilate normal bronchi. They demonstrated bronchographically that immediate bronchial dilatation occurs when lobar collapse is induced in a healthy cat. Continuing their investigations, they studied cases of "black lobe." In certain cases of pulmonary tuberculosis in which treatment with artificial pneumothorax is being carried out, a sudden massive collapse of the partially collapsed lung sometimes occurs, producing the condition known from its appearance in the roentgenogram as "black lobe." Lander and Davidson demonstrated the presence of bronchial dilatation in such cases and its disappearance with an adequate refill of air. They repeated this procedure in ordinary cases of pulmonary collapse, with identical results. Furthermore, Ochsner,[26] Jennings [27] and Lander and Davidson reported cases of temporary atelectatic bronchiectasis. A definite atelectatic shadow, within which dilated bronchi were demonstrated, was studied by serial roentgenograms. Disappearance of the "collapse" shadow was accompanied by a return to normal of the bronchial caliber.

A case in my personal observation which bears on this point may be recorded here.

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24. Hedblom, C. A.: Surg., Gynec. & Obst. **52**:406, 1931.
25. Laennec, R. T. H.: De l'auscultation médiate, Paris, J. A. Brosson & J. S. Chaudé, 1819, vol. 1, p. 124.
26. Ochsner, A.: Am. J. M. Sc. **179**:388, 1930.
27. Jennings, G. H.: Brit. M. J. **2**:963, 1937.

Mrs. G., a married woman of 34, was suddenly taken acutely ill, with breathlessness, high fever and pain in the left side of the chest. When seen ten days later, she was stated to be rather better. She was expectorating purulent sputum, but was still breathless on slight exertion. Examination of the chest revealed that the apex beat was in the left midaxillary line and that the left side of the chest was dull. Breathing was cavernous or tubular, and crackling rales were generalized over the left lung. The roentgenogram and bronchogram are reproduced. She was regarded as too ill to undergo a bronchoscopic examination at that time, and other measures directed toward securing reexpansion of the lung were employed. The abnormal signs did not disappear until three months later, when the last roentgenograms were taken.

Attention is directed to the opacity of the lung, with the presence of "cavities" in the early exposures, and the tortuosity and dilatation of the bronchi. In 1 instance iodized poppy seed oil entered the cavity, although it was prevented by obstructive secretions from entering the others. The later roentgenograms show restoration to normal.

This case appeared to be one of massive collapse of the lung associated with bronchial dilatation, which disappeared when the lung reexpanded.

It therefore becomes evident that the rise of intrabronchial pressure consequent on pulmonary collapse can produce dilatation of normal bronchi. How much more readily will such a force dilate bronchi weakened by disease?

Persistent coughing was advanced as a cause of increased intrabronchial pressure which might act as a dilating force, but the suggestion was refuted by Hedblom and by MacCallum,[28] who pointed out that pressure due to coughing is counteracted by the resistance of the diaphragm and of the chest wall.

Finally, extensive parenchymal scarring as a cause of bronchiectasis was ably advanced by Corrigan,[28] who expressed the belief that counteracting scar tissue might dilate the bronchi by traction. This view received recent support from Findlay and Graham,[29] but in general finds little credence at present. Pathologic evidence does not support it. Bronchiectasis can exist without significant scarring,[30] and extensive fibrosis is not infrequently seen without bronchiectasis, as in certain cases of tuberculous and nontuberculous pulmonary fibrosis.

In the present series the stellate appearance of the bronchial lumen, described by Opie, was regularly observed when bronchial destruction was pronounced. It could not, however, be attributed to contraction of parenchymal scar tissue, for it occurred when this was slight or absent. Furthermore, when scarring was present, the collagenous strands were peribronchial and did not run in bands from bronchus to bronchus or outward to unite with pleural scar tissue.

28. Corrigan, D. J.: Dublin J. M. Sc. **13**:266, 1838.
29. Findlay, L., and Graham, S.: Arch. Dis. Childhood **2**:71, 1927.
30. Robinson.[15] Sauerbruch.[17] Lander and Davidson.[18]

A more likely way in which pulmonary scarring might act is by weakening the support of the bronchi, through its replacement of the normal, functioning lung tissue, in much the same way as was just described in the discussion of atelectasis. MacCallum emphasized the possible dilatation produced by expiration against resistance, such as is likely to occur when a partial bronchial obstruction, due to stenosis of the bronchus or pressure from without, acts on a weakened bronchial

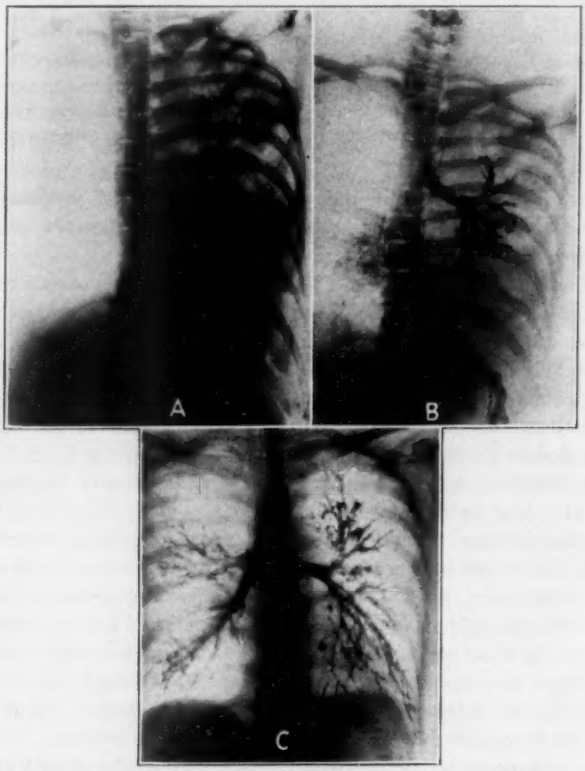

Fig. 15.—*A*, a roentgenogram of Mrs. G. made in May 1938. Note the general opacity of the pulmonary field and the numerous "cavities" within the field. The heart and trachea are displaced to the left. *B*, a bronchogram of Mrs. G. made in May 1938. Note the tortuosity and irregular dilatation of the bronchi. No iodized poppyseed oil has entered the "cavities" or the finer bronchi, which are evidently obstructed. *C*, a second bronchogram of Mrs. G. made in August 1938. The appearance of the bronchial tree is normal. The heart and trachea have returned to a normal position, and the opacity and "cavitation" have disappeared from the left pulmonary field.

wall. This possibility again is theoretic and has neither been proved nor disproved. It is undoubtedly possible that such dilatation does occur, but it is unlikely that it is at all frequent. As will be seen in the following section on etiology, bronchial obstruction is a frequent predisposing factor in bronchiectasis, but seems to act more often by favoring collapse or by hindering the removal of infection.

Comment: It appears from the foregoing evidence and general argument that weakening of the bronchial wall is frequent in bronchiectasis and that various strains and stresses may act on it as a dilating force, under abnormal conditions, whether it is weakened or no. The chief of these, and the only one the action of which has as yet been proved, is pulmonary collapse.

How is bronchial dilatation actually produced?

It has become obvious that no arbitrary answer can be accepted.

A damaged, and therefore weakened, bronchial wall is potentially liable to dilatation, but such dilatation need not necessarily occur. Any significant increase in the normal intrabronchial pressure will, however, cause the bronchus to dilate. Such a dilating force may be any of those which have previously been mentioned, and bronchiectasis can thus be produced in various ways. Furthermore, normal bronchi will dilate when subjected to excessive strain and will remain dilated until this strain is removed.

One must, therefore, recognize the probable existence of cases of chronic bronchial infection in which dilatation has not occurred, but is liable to occur. In such cases the patient must be watched. Cases in the present series which support this view will be described in the section on the roentgenographic features. These are instances of apparent "spread" of bronchiectasis, such as were recorded by Roles and Todd.[31]

On the other hand, bronchial dilatation does not necessarily mean that the bronchi are diseased, and the differentiation of the cases in which disease is lacking is important if unnecessary operations are to be avoided. Lander and Davidson were insistent on this point. Although evidence has been adduced which minimizes the probable frequency of such cases, the obligation to recognize their existence remains.

The cause of bronchial dilatation in those cases in the present series in which the excised lobes were placed in the bronchopneumonic group must be referred to before closing this section. In those, it will be remembered, bronchial destruction was more advanced, as a rule, and in none was damage slight. They were all cases in which parenchymatous changes were prominent, and the view is taken that the seriously weakened bronchi were in this way partially deprived of their main resistance to dilatation, namely, the normal aeration of the peribronchial alveoli.

31. Roles, F. C., and Todd, G. S.: Brit. M. J. **2**:639, 1933.

Other forces, such as the weight of retained secretions, the obstruction to expiration which these would cause (of MacCallum) and localized areas of collapse, may also have played a part. Furthermore, in a few cases areas of actual excavation of the lung were seen. The bronchial wall was completely deficient in one place, the margin of the lumen being formed only by lung tissue at this point. This condition resulted from a cavitation process rather than from true dilatation, perhaps, but is worthy of mention.

CONGENITAL BRONCHIECTASIS

There is a well defined and widely recognized congenital bronchial anomaly which is generally known as "congenital cystic disease of the lung." Two cases in the present series were regarded as instances of this abnormality, although the diagnosis was not asserted with certainty, owing to the absence of an autopsy in either case. It is no doubt true, as Warner [32] and Kartagener [33] showed, that cases are, from time to time, erroneously regarded as examples of congenital cystic disease, but this fact does not affect the established existence of the condition. Many cases are now on record in which the true nature of the disease was verified by actual examination of the affected organs. The reports of Koontz,[34] Schenck,[35] Fleming,[36] Croswell and King,[37] Hennell [38] and others are conclusive.

The mode of origin is still in dispute, but the general view seems to support the theory that the abnormality is a failure of canalization of the smaller or terminal bronchioles, with arrested development of the corresponding area of lung, which becomes cystic. These cysts may be single or multiple and at birth are filled with a milky, opalescent fluid similar to or identical with the contents of the fetal bronchial system. Later this fluid may be expelled and the cysts remain as air cysts or become infected. A case in which infection occurs may be difficult or impossible to distinguish clinically and even pathologically [32] from acquired bronchiectasis, but the cases in which infection is lacking do not suggest bronchiectasis.

It is indeed debatable whether this anomaly should be classed as bronchiectasis at all. No less an authority than Sauerbruch,[39] however, has advanced the view that a considerable number of cases in which there

32. Warner, W. P.: Quart. J. Med. **3**:401, 1934.

33. Kartagener, M.: Beitr. z. Klin. d. Tuberk. **85**:45, 1934.

34. Koontz, A. R.: Bull. Johns Hopkins Hosp. **37**:340, 1925.

35. Schenck, S. G.: (*a*) Am. J. Roentgenol. **35**:604, 1936; (*b*) Diagnosis of Congenital Cystic Disease of the Lung, Arch. Int. Med. **60**:1 (July) 1937.

36. Fleming, G. B.: Arch. Dis. Childhood **9**:201, 1934.

37. Croswell, C. U., and King, J. C.: Congenital Air Cyst of Lung: Report of Case, J. A. M. A. **101**:832 (Sept. 9) 1933.

38. Hennell, H.: Cystic Disease of Lung, Arch. Int. Med. **57**:1 (Jan.) 1936.

39. Sauerbruch, F.: Arch. f. klin. Chir. **180**:312, 1934; footnote 17.

is all the appearance of bronchial dilatation without the presence of cysts are in reality instances of congenital bronchial deformity. In such cases the bronchi would, of course, be liable to secondary infection, although he did not stress this point. When the difficulty of differentiating congenital cystic disease in the presence of infection is admitted, the difficulty which is likely to arise in the recognition of Sauerbruch's "congenital type" may be imagined.

Sauerbruch described a series of 50 cases in which infection was apparently insignificant. Lotzin, who with Sauerbruch examined the lobes excised in these cases, reported that histologic appearance as follows:

The bronchial epithelium was ciliated and consisted of several layers. The muscle was irregular and was hypertrophied, while only irregular strings of elastica were seen. The bronchi were described as "ending blindly," without alveolar connections. Mucous glands were abnormally numerous, and cartilage was poorly developed. There was "no sign of inflammation, past or present."

In all these cases the patients were children and the disease in each case was confined to one lobe, nearly always the lower lobe of the left lung. Sauerbruch expressed the belief that this is the rule in cases of this type, but when one compares his series with 381 cases of congenital cystic disease collected by Schenck, confidence is shaken. In Schenck's cases the disease was right sided in 157 and left sided in only 136, while it was bilateral in 78.

Sauerbruch [17] explained the left-sided unilobar incidence in his cases embryologically. In the fifth week of fetal life [40] the thoracic cavity enlarges and the ducts of Cuvier, running in the septum transversum, elongate and enter the sinus venosus at a much more acute angle. At this period the lung buds are growing rapidly, and Sauerbruch expressed the belief that in certain cases the left duct in particular presses on the embryonic lung, interfering with the development of that portion which forms the lower lobe. This appears to be a reasonable hypothesis, once the congenital origin of lobar bronchiectasis is established.

No other author, however, as far as was discovered, confirmed the histologic observations of Sauerbruch and Lotzin. The evidence in the literature which has been cited emphasized the changes produced by infection, with the exception of that of Lander and Davidson, who nevertheless discovered no indication of congenital bronchial defect. The material examined in the present study also failed to reveal similar changes.

This statement is, of course, quite another thing from a denial of the existence of Sauerbruch's "congenital type," and no such denial is contemplated. The negative evidence suggests that the frequency of its

40. Keith, A.: Human Embryology and Morphology, ed. 4, London, E. Arnold, 1921, p. 346.

occurrence is less than Sauerbruch stated, but, in fact, the root of the matter is that the existence of congenital defects in a seriously damaged bronchus is as difficult to disprove as to prove.

Evidence of associated congenital defects is to be found in the literature. Kartagener [38] reported cases of congenital heart disease and situs inversus in association with bronchiectasis and met with instances of familial bronchiectasis. There is a possibility that the bronchiectasis in these cases was secondary to the abnormal cardiac condition. Congenital heart disease is recognized as a cause of pulmonary collapse, and I saw several cases in which this relation existed.

A report of congenital abnormalities of the nasal sinuses in cases of bronchiectasis was also suggestive, although it must be admitted that such evidence is mainly circumstantial.

A large literature has grown up around the subject of congenital bronchial defect, and although the great majority of the articles deal with congenital cysts of the lung, whether single or multiple, no solution has been found for the problem under discussion. It is believed that a fair presentation of the position has been made, and further discussion is considered unnecessary. Neither the occurrence or frequency of congenital bronchiectasis nor its true relation to congenital cystic disease of the lung can be established on the evidence at present available. Evidence which seems opposed to the existence of a "congenital type" is also of suggestive value only, and the matter must, perforce, be left open.

ETIOLOGY

Etiology and pathogenesis have usually been discussed together in the literature on bronchiectasis, and it is felt that this may have contributed to a certain confusion as to the causation of this condition.

Therefore it seemed desirable in this essay first of all to establish as well as possible the mode or modes of pathogenesis and then to discuss the etiology in the light of this.

With regard to indirect etiologic factors, no particular sex incidence could be determined, but the question of age was found to be important. The age of onset was not as a rule dealt with statistically, as writers concentrated rather on the age at which their patients were first seen. Farrell,[41] however, stated that 80 per cent of his patients dated their symptoms from the first decade of life, and my experience with the present series is even more emphatic as regards the early onset of symptoms.

In 45 of my 68 cases, or 66 per cent, symptoms dated from the first five years of life, and in 37 of the 45, from the first two years. In only

41. Farrell, J. T., Jr.: Importance of Early Diagnosis in Bronchiectasis: Clinical and Roentgenologic Study of One Hundred Cases, J. A. M. A. **106**:92 (Jan. 11) 1936.

23 cases, or 34 per cent, was there a history of later onset, and even in a number of these symptoms dated from late childhood. It is, of course, impossible to say whether bronchial dilatation was present throughout the intervening period, but it is at least obvious that the processes which produced it were in operation. It must be emphasized that symptoms of one sort or another were constantly present in all cases.

Bronchiectasis, in its origin, is therefore to an important extent a disease of childhood, quite apart from "congenital predisposition." The infinitely better results attending active medical treatment and operation in childhood increase the significance of this fact, since if in two thirds of all cases the condition has its origin in childhood, early recognition should greatly improve prospects for the treatment of the disease as a whole.

Bronchiectasis is a disease of those parts of the world in which infections of the respiratory tract are particularly common. Nothing further need be said as to the indirect etiologic factors.

The direct etiologic factors can readily be assessed from the foregoing account of the pathogenesis. They may be conveniently divided into the following groups:

Causes of bronchial damage:

1. Infections of the bronchopulmonary system and other direct causes.
2. Any conditions which predispose to the occurrence or recurrence of such infections.
3. Factors favoring the persistence or extension of bronchial infection.

Causes of abnormal bronchial strain:

1. All causes of lobar or pulmonary collapse and all conditions predisposing thereto.
2. Causes of parenchymal damage or destruction.
3. Factors favoring the retention of large amounts of weighty secretions within the bronchi.

CAUSES OF BRONCHIAL DAMAGE

Infections.—Almost any infection of the respiratory tract, of which the most obvious example is bronchopneumonia, can be included under this heading. It is important to recognize, however, that the original infection may be comparatively slight in its general effects, a fact accounting for the apparently "spontaneous" origin of symptoms, observed in 29 cases (43 per cent) of my series. As will be demon-

strated in the section on clinical features, this figure agrees well with that for most of the reported series.

The bacteriologic studies on bronchiectasis are not helpful, and a review of the literature forces one to the conclusion that any organism which is known to produce lesions in the respiratory tract may be concerned. Leys [42] stressed the importance of Pfeiffer's bacillus, and Blake and Cecil [43] and Opie and his associates [44] also accused this germ, the former on experimental grounds. Smith [45] and Pilot and Davis,[46] on the other hand, claimed both on clinical and on experimental grounds that Vincent's spirochete is a frequent cause of bronchial damage leading to bronchiectasis. An extensive study by Greey [47] seemed to prove conclusively, however, that the great variety of organisms which may be found precludes any idea of a specific or predominating bacterial cause.

Extensive bacteriologic studies were not carried out in the present series, owing to Greey's conclusions. Tubercle bacilli were, however, consistently sought, with uniformly negative results.

Caution must always be observed in accepting without reserve the patient's statement of a history of a previous thoracic disease, as the diagnosis cannot be verified. However, the surveys of etiologic factors in the literature and in the present series were necessarily based on such histories and must be accepted for what they are worth. The results of these surveys were difficult to compare, because each author seemed to adopt a different grouping, but the constancy of a particularly high incidence of previous disease of the respiratory tract with a definite chronologic relation to the onset of symptoms was extremely suggestive.[48] This incidence was over 50 per cent, and the diseases most frequently mentioned were pneumonia, bronchopneumonia, bronchitis and influenza. Measles and whooping cough came low on the list. A comparison with the incidence in the present series may be of interest.

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42. Leys, D.: Chronic Pulmonary Catarrh, London, H. K. Lewis & Co., Ltd., 1927.

43. Blake, F. G., and Cecil, R. L.: J. Exper. Med. **32**:691, 1920.

44. Opie, E. L.; Freeman, A. W.; Blake, F. G.; Small, J. C., and Rivers, T. M.: Pneumonia Following Influenza, J. A. M. A. **72**:556 (Feb. 22) 1919.

45. Smith, D. T.: Am. Rev. Tuberc. **15**:352, 1927; Etiology of Primary Bronchiectasis, Arch. Surg. **21**:1173 (Dec., pt. 1) 1930; J. Infect. Dis. **46**:303, 1930.

46. Pilot, I., and Davis, D. J.: Studies in Fusiform Bacilli and Spirochetes: Their Rôle in Pulmonary Abscess, Gangrene and Bronchiectasis, Arch. Int. Med. **34**:313 (Sept.) 1924.

47. Greey, P. H.: J. Infect. Dis. **1**:302, 1932.

48. (*a*) Fletcher, E.: J. Thoracic Surg. **4**:460, 1935. (*b*) Thorpe, E. S.: Am. J. M. Sc. **177**:759, 1929. (*c*) Hedblom.[24] (*d*) Farrell.[41] (*e*) Ballon, Singer and Graham.[18] (*f*) Findlay and Graham.[29]

	Cases		Cases
Bronchopneumonia	22	Primary	19
		Measles	2
		Whooping cough	1
Lobar pneumonia	1		
Bronchitis	14	Primary	7
		Whooping cough	4
		Influenza	2
		Rubella (?)	1
Insidious, or "spontaneous" onset	29		

Influenza was less important and measles and whooping cough rather more important than in other series. The predominant position of bronchopneumonia was fully supported, however.

Murphy [49] and others reported an area of bronchiectasis at the site of a primary tuberculous lesion, and Eliasberg and Neuland [50] noted bronchiectasis in cases of epituberculosis.

Pulmonary abscess was often mentioned as a cause of bronchiectasis. This condition is really covered by what has already been said, as it is an infection of the respiratory tract. But Ballon, Singer and Graham [18] stated that "chronic abscess" is always followed by bronchiectasis, and Warner reported that in 12 per cent of his cases the bronchiectasis was due to "lung abscess." [11] Without further examination, one would expect this condition to be a causative factor, since pulmonary destruction occurs. No case has actually been met with personally, but perhaps this was because patients who did not recover under medical treatment were operated on and their cases might not, therefore, come under the heading of "chronic" abscess. (Maxwell,[51] however, in a large series of 315 cases found only 5 cases of bronchiectasis.) The evidence is thus conflicting, but it would appear that pulmonary abscess must be regarded as at least an occasional cause of bronchiectasis.

The recently imported condition of "pneumonitis" must also be mentioned, because a suppurative variety was recently described by Garland and Berridge [52] as resulting in bronchiectasis in 2 out of 16 cases. The true existence of "pneumonitis" cannot be freely admitted in the absence of a pathologic basis, but reference to it cannot be omitted in view of numerous recent reports. I offer it as a possibility that these cases of "pneumonitis" may be instances of acute or suppurative bronchiolitis associated with instances of lobular collapse. The diagnosis, at present, appears to rest on the appearance of the roentgenograms.

Norris and Landis [53] insisted on the importance of inorganic dust as a cause of bronchial damage leading to bronchiectasis. They found

49. Murphy, J. E.: Am. J. Roentgenol. **31**:301, 1934.
50. Eliasberg, H., and Neuland, W.: Jahrb. f. Kinderh. **93**:88, 1920.
51. Maxwell, J.: Quart. J. Med. **3**:467, 1934.
52. Garland, A., and Berridge, F. R.: Lancet **1**:375, 1939.
53. Norris, G. W., and Landis, H. R. M.: Diseases of the Chest, ed. 4, Philadelphia, W. B. Saunders Company, 1929.

that of 21 potters examined by them 10 showed bronchiectasis. This number is greater than I have had the opportunity of studying, as silicosis is rather uncommon in the north of England. In 2 cases of silicosis, however, the bronchi were normal. War gases were described by Farrell [41] and Fletcher [41a] as an occasional cause of bronchiectasis; here, again, I am unable to confirm this observation, owing to an insufficient number of cases. In 5 cases of chronic disability following gassing in the World War, however, the patients all showed normal bronchi. No cases of bronchiectasis due to inorganic causes were met with, therefore, but no intensive search for such cases has as yet been attempted.

Predisposing Factors.—Certain of the specific infectious fevers, particularly influenza, measles and whooping cough, are widely recognized as predisposing to the development of bronchopneumonia, although this association was noted in only 3 cases in the present series. Pink disease also appears to predispose to infection of the respiratory tract and bronchiectasis on occasion.[54]

As a direct cause of the occurrence and recurrence of infection of the respiratory tract, great importance is attached in the literature to chronic sinusitis. A large number of articles have been devoted to the relation between chronic sinusitis and bronchiectasis, only a few of which can be referred to here. The generally accepted theory of sinusitis as a cause of bronchiectasis is that of the repeated direct aspiration of infective products from the nasal passages. This provides a continual reenforcement of an existing infection, even if it is not actually the origin of the primary infection itself.

Quinn and Meyer [55] introduced iodized poppyseed oil into the nasal passages during sleep. Subsequent roentgenographic examination showed iodized oil in the lungs in 5 of 11 persons. These authors also found sinusitis in 22 out of 38 cases of bronchiectasis.

Mullin [56] expressed preference for the theory of spread of infection through the lymphatics from the antrum to the main lymph ducts, and so by the great veins to the lungs. This idea has not gained general acceptance, and the theory of aspiration seems to be the most likely one.

Graham [57] and Thomson [58] both noted the association of sinal infection with bronchorrhea. Graham made numerous observations on bronchial fistulas and noted that there was an immediate inflammatory

54. Spence, J. C.: Personal communication to the author.

55. Quinn, L. H., and Meyer, O. O.: Relationship of Sinusitis and Bronchiectasis, Arch. Otolaryng. **10**:152 (Aug.) 1929.

56. Mullin, W. V.: Ann. Otol., Rhin. & Laryng. **30**:685, 1921.

57. Graham, E. A.: Surgical Treatment of Pulmonary Suppuration in Children, J. A. M. A. **87**:806 (Sept. 11) 1926.

58. Thomson, St. C.: Practitioner **92**:745, 1914.

reaction at the fistula when any exacerbation of the sinal infection occurred. Rist [59] found an association of sinal infection with cough.

Sergent [60] was the first to draw attention to the clinical connection between infections of the upper and those of the lower respiratory tract, and a great deal has been written on this subject since his article, published in 1916.

Webb and Gilbert,[61] in a roentgenographic study of all the sinuses in cases of disease of the chest, found that in only a few cases of bronchiectasis was there no evidence of chronic infection of the accessory sinuses. Bilateral empyema of the antrums was the lesion most frequently encountered. Other communications were made by Dennis,[62] Davis,[63] Young,[64] Moll,[65] Ballon, Singer and Graham [18] and others. The most recent series, and the largest, was that of Walsh and Meyer.[66] Of 217 cases of bronchiectasis, there was associated sinusitis in 45, or 66.8 per cent. No relation between the severity of the sinusitis and the extent and duration of the bronchiectasis could, however, be established. Symptoms referable to the sinusitis were unusual. The sinuses were especially and fully examined in each case in an active search for infection, and a diagnosis of sinusitis was made only when gross pus was demonstrable in one or more of the sinuses.

On the pathologic side, reference may be made to papers by Opie [67] and by Ebbs.[68] In a review, Opie recorded that sinal infection is almost always found in patients with influenzal pneumonia and that influenza may be a prebronchiectatic condition. Ebbs found evidence of sinusitis or otitis at autopsy in 86 per cent of 200 cases of pneumonia.

What conclusion is one to draw from this mass of evidence? It would seem reasonably clear from the aforementioned reports that infective material can and does reach the bronchi from the nasal sinuses and often gives origin to or exacerbates bronchial infection. It also appears probable that in patients who are expectorating large amounts of purulent sputum daily the reverse process is likely to occur. The literature offers no evidence which enables one to differentiate between these two possibilities, and it seems reasonable that infection occurs in

59. Rist, E.: Rev. de la tuberc. **7**:705, 1926.

60. Sergent, E.: Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1424, 1916.

61. Webb, E. B., and Gilbert, G. B.: Bronchiectasis and Bronchitis Associated with Accessory Sinus Disease, J. A. M. A. **76**:714 (March 12) 1921.

62. Dennis, F. L.: Ann. Otol., Rhin. & Laryng. **33**:451, 1924.

63. Davis, E. D. D.: J. Laryng. & Otol. **43**:495, 1928.

64. Young, R. A.: J. Laryng. & Otol. **43**:470, 1928.

65. Moll, H. H.: Quart. J. Med. **1**:457, 1932.

66. Walsh, T. W., and Meyer, O. O.: Coexistence of Bronchiectasis and Sinusitis, Arch. Int. Med. **61**:890 (June) 1938.

67. Opie, E. L.: The Pathologic Anatomy of Influenza, Arch. Path. **5**:285 (Feb.) 1928.

68. Ebbs, J. H.: Proc. Roy. Soc. Med. **30**:1407, 1937.

both directions. Data from the present series do not suggest any solution of the problem because of the inadequate number of cases in which the patient was subjected to full investigation, including proof puncture. In only 13 of the 68 cases could sinusitis be proved, and in all these it was antral. It is suggested here that the sinusitis is in many cases secondary, but that once established it may cause repeated reinfection of the bronchi, setting up a vicious circle. The observed fact that the vast majority of sinal infections associated with bronchiectasis are antral supports this view.

Unfortunately, no authors were able to point to any improvement in the condition in the chest after treatment of the nasal infection, and this experience is corroborated by the few cases in the present series. It would appear that the most reasonable attitude for the future is to search for sinal infection in all cases of bronchiectasis in which operation is to be performed and to deal adequately with such infection after operation, in order to prevent further damage. This practice is now being carried out, I understand, in the department of thoracic surgery at the Newcastle General Hospital.

Chronic tonsillitis was not found by other authors to have any particular association with bronchiectasis, and none was noted in the present series.

Factors Favoring the Persistence or Extension of Bronchial Infection.—The chief of these factors is bronchial obstruction. If a bronchus is obstructed, drainage is hindered, and the tubes distal to the obstruction cannot adequately rid themselves of infective products. These, if retained, continue and may extend the process of bronchial damage.

Eloesser,[69] in a detailed study of bronchial obstruction, emphasized its importance in the production of bronchiectasis and classified its causes under three heads: intramural, mural and extramural. With regard to the intramural causes, the effects of foreign bodies within the bronchi are well known and need only be mentioned. There was only 1 illustration of this in the present series, the case of a boy who inhaled a portion of a walnut into his trachea. An attempt at removal of the nut, which was balanced at the carina, resulted in a portion entering the left bronchus. Bronchiectasis of the lower lobe of the left lung resulted.

Of recent years, particular attention has been directed to the obstructive effect of viscid bronchial secretions, due in most cases, though perhaps not in all, to bronchial infection. Chevalier Jackson[70] demonstrated this phenomenon repeatedly by aspirating viscid mucopurulent material from the bronchi in cases of postoperative atelectasis, with resultant reexpansion of the collapsed lung or lobe.

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69. Eloesser, L.: J. Thoracic Surg. **1**:485, 1932.
70. Jackson, C.: (*a*) Proc. Roy. Soc. Med. **24**:1, 1930; (*b*) footnote 6.

The presence of a bronchial adenoma may also cause gross bronchial obstruction with collapse of the lung and resultant bronchiectasis. I met with 1 example of this, in a patient whose case was not included in the present series. No lobectomy has been performed on the patient, who suffered from a suppurative bronchial infection which subsided after removal of the adenoma.

Mural obstruction consists mainly of bronchial stricture, which may be inflammatory or neoplastic. Inflammatory stricture may result from local trauma and secondary infection, theoretically, or from tuberculous or syphilitic ulceration. Tuberculous bronchial stenosis was reported by Eloesser,[71] Cohen and Higgins,[72] Phelps,[73] Bucher[74] and others. Cohen and Higgins reported 19 cases, in 13 of which bronchiectasis was proved and in 4 of which symptoms were present, though bronchiectasis was not demonstrated. Bucher described a case of inflammatory bronchial obstruction due to tuberculosis, and Andrews[75] observed similar cases. Lightwood and Wilson[76] demonstrated a case of bronchiectasis associated with bronchial stenosis in a boy of 5 who had a strongly positive tuberculin reaction. Recently Morlock and Hudson[77] published a brief but interesting account of their experiences with bronchoscopy in cases of pulmonary tuberculosis. They found that obstructive lesions were not infrequent and divided the cases in which there was obstruction into four groups:

1. Those in which the obstruction appears to be due to an enlarged gland, or tuberculoma. [This group is discussed later.]

2. Those in which gelatinous tuberculous granulations obstruct the bronchus.

3. Those in which pulmonary fibrosis with resulting deformity of the bronchus cause the block.

4. Those in which the bronchial mucous membrane is so edematous as to cause narrowing of the lumen, which is filled with tenacious secretion.

Syphilitic bronchial stenosis was studied by Conner,[78] who found 15 examples of bronchiectasis in 128 collected case reports. The presence of this condition in all of these cases was proved bronchoscopically, except in Conner's own cases, in which it was verified at autopsy.

In the present series, no examples of tuberculous stenosis were found, although it is true that in several of the cases there was no bronchoscopic examination. A positive Wassermann reaction was reported in 3 cases, but no evidence of stricture was found, although in

71. Eloesser, L.: Am. Rev. Tuberc. **30**:123, 1934.
72. Cohen, S. S., and Higgins, G. K.: Am. Rev. Tuberc. **36**:711, 1937.
73. Phelps, K.: Ann. Otol., Rhin. & Laryng. **45**:1133, 1936.
74. Bucher, C. J.: Pulmonary Tuberculosis Associated with Acute Bronchial Obstruction, J. A. M. A. **90**:1289 (April 21) 1928.
75. Andrews, C. H.: Canad. M. A. J. **33**:36, 1935.
76. Lightwood, R., and Wilson, R.: Arch. Dis. Childhood **11**:321, 1936.
77. Morlock, H. V., and Hudson, E. H.: Brit. M. J. **1**:381, 1939.
78. Conner, L. A.: Am. J. M. Sc. **126**:57, 1903.

1 case a syphilitic ulcer of the vocal cords was present. In all 3 cases a bronchoscopic examination was made.

Adams and Escudero [79] claimed to have proved that bronchiectasis occurs only if the obstruction is incomplete, and it seems reasonable to suppose that aerobic infection is unlikely to progress if the obstruction is complete. These authors worked with dogs and did not find bronchiectasis with atelectasis resulting from complete obstruction. This information cannot be accepted as applying to human beings. In any event, the observations at autopsy were not conclusive. It is known that dilatation is only temporary in cases of bronchial obstruction, unless bronchial destruction has occurred.

As regards the present problem, Adams and Escudero seem to have shown that infection does not persist when obstruction is complete. They produced bronchial stricture in dogs by means of either thermal cauterization or a solution of silver nitrate and then introduced cultures from an abscess of a human lung. Bronchiectasis occurred in all 15 dogs within six weeks, except in 1 which died of distemper on the third day. They next introduced the culture suspended in iodized poppyseed oil and found no bronchial damage in five weeks. The choice of iodized oil seems rather unfortunate, owing to its known antiseptic properties, but the evidence is strongly suggestive. Clinically, however, it is probable that obstruction is rarely absolute for more than a short time, as, even with a foreign body, secretions can be expelled by coughing. It is more likely that obstruction is either partial or valvular, allowing a little air to enter, while preventing its exit during quiet expiration. This air may be insufficient to reinflate a collapsed lobe, although perhaps increasing bronchial pressure slightly. But it will yet be adequate, in all probability, to nourish the intrabronchial infection.

Extramural obstruction is caused typically by pressure of an aortic aneurysm or a mass of malignant glands, as is well recognized. An interesting and less widely appreciated cause of extramural obstruction is pressure by tracheobronchial or bronchopulmonary lymph nodes which have enlarged because of tuberculous infection. Vinson [80] described bronchiectasis due to this type of extramural obstruction, and de Bruin [81] noted atelectasis, but did not mention bronchiectasis. A bitonal cough and the expiratory stridor which accompany such obstruction were described by Wallgren,[82] in a classic article on infantile primary tuberculosis.

One example of bronchiectasis due to extramural obstruction occurred in the present series. This was the case of a man of 27 who

79. Adams, W. E., and Escudero, L.: Tubercle **8**:351, 1938.
80. Vinson, P. P.: M. Clin. North America **19**:453, 1935.
81. de Bruin, M.: Arch. Dis. Childhood **11**:65, 1936.
82. Wallgren, A.: Primary Pulmonary Tuberculosis in Childhood, Am. J. Dis. Child. **49**:1105 (May) 1935.

complained of persistent cough and purulent expectoration, of four years' duration. He had had pleurisy five years before and a "feverish cold" four years before and dated his symptoms from the latter. He was found to have bronchiectasis of the middle lobe of the right lung, and died within twenty-four hours of an operation on his chest. At autopsy, evidence of healing tuberculosis was noted in the upper lobe of the right lung, and the bronchopulmonary and hilar glands were greatly enlarged. These glands appeared to be pressing on the bronchus leading to the middle lobe of the right lung, so that the lumen was greatly narrowed.

Tuberculosis is thus far from being an unimportant factor in the causation of bronchiectasis, and Potter [83] expressed the opinion that the incidence of "bronchiectasis associated with chronic fibro-ulcerative lesions is high." It is chiefly as a cause of bronchial obstruction that tuberculosis appears to act, although Murphy's [49] report of bronchiectasis at the site of a primary tuberculous lesion and Eliasberg and Neuland's observation of bronchiectasis in epituberculosis have already been cited.

From the foregoing discussion it appears that bronchial obstruction is an important cause of bronchiectasis, but that incomplete obstruction is a more potent factor than is complete obstruction in the propagation of infective bronchial damage. One further possible cause of the persistence of a bronchial infection must be referred to. As has been mentioned before, it seems probable that superficial but extensive bronchial infection may paralyze or hinder the normal bronchial function of the expulsion of foreign material, and so favor the retention of infective products, with consequent persistence and extension of bronchial infection. This probability cannot be proved, but the experiments of Hudson and Jarre,[8] which were cited in the section on anatomy and physiology, offer indirect evidence. The probability is mentioned as a deduction from what is known of the normal bronchial function.

CAUSES OF ABNORMAL BRONCHIAL STRAIN

1. *All Causes of Lobar or Pulmonary Collapse and All Conditions Predisposing Thereto.*—The prime cause of collapse of the lung is bronchial obstruction, which must be of sufficient severity to prevent the entry of air. Lichtheim [84] demonstrated that the air within the part of the lung distal to the obstruction was then absorbed, allowing the lung to collapse.

All the causes of bronchial obstruction which were described in the preceding section are therefore likely to be causes of collapse, provided they fulfil this condition; that is, they must exclude air from the part of the lung distal to the obstruction. This is rather a matter of the

83. Potter, B. P.: Am. J. Roentgenol. **31**:308, 1934.
84. Lichtheim (quoted): Arch. f. exper. Path. u. Pharmakol. **10**:54, 1878.

degree of obstruction in any particular case than of the origin of the obstruction itself, although, of course, certain types of obstruction are more likely to be complete than others.

Several causes of obstruction must, however, be accorded special consideration. The first of these is obstruction by intrabronchial secretion, which was emphasized as a cause of postoperative collapse on experimental and clinical grounds by Band and Hall [85] and by Elliott and Dingley.[86] It is true that this condition was mentioned in the preceding section, but, owing to its special importance in the present connection, something further must be said. The history and usual clinical course have been described in a previous communication.[87] Briefly, the condition is one of bronchitis or bronchiolitis, in which the bronchi of a lobule, a lobe or a lung become acutely infected and inflamed, with consequent swelling of the mucosa and production of a viscid secretion, which together block the lumen. Collapse of the corresponding area of the lung distal to the obstruction occurs, and this collapse may be lobular, lobar or pulmonary, according to the grade and number of the obstructed bronchi or bronchioles. Such obstructions occur typically after abdominal operations, but there can be little doubt that they occur "spontaneously" much more frequently.

Any illness causing or associated with bronchitis can cause collapse, such as measles, whooping cough or influenza. Few cases in the present series were instances of atelectatic bronchiectasis following whooping cough. In the great majority of cases, recovery with complete reexpansion of the collapsed lung, takes place in a few days, usually after the expectoration of a varying amount of sticky, mucopurulent sputum.

For this reason, in few such cases do the patients attend a hospital, and in fewer still are they studied roentgenographically. The true condition is thus readily overlooked, and the illness is apt to be diagnosed as "abortive pneumonia."

In a proportion of cases, however, the failure of this early reexpansion to occur is due in all probability to a more persistent infection or to inefficient breathing from any cause or to both of these together.

From the studies of Lander and Davidson,[18] it is known that bronchial dilatation is almost certain to be present as long as the collapsed state persists, and the after-history then depends on two factors: the dose and virulence of the infecting organisms and the duration of the collapse. The longer the lung remains collapsed, the more likely is bronchial dilatation to become permanent. The case reported in the section on pathogenesis shows that restoration to normal is possible even after several months and that reexpansion can be assisted by suitable

85. Band, D., and Hall, I. S.: Brit. J. Surg. **19**:387, 1932.
86. Elliott, T. R., and Dingley, L. A.: Lancet **1**:1305, 1914.
87. Ogilvie, A. G.: Newcastle M. J. **15**:30, 1935.

measures, but every effort should be made to recognize and deal with the condition at an early date, if permanent bronchiectasis is to be avoided. The high incidence of atelectatic bronchiectasis in the present series supports the view that "spontaneous" collapse of the lung is an important cause of bronchiectasis.

Traumatic collapse was studied by Bradford,[88] who emphasized the frequency of contralateral collapse, which suggests some reflex action. A reflex mechanism was proposed by Scott [89] as a cause of postoperative atelectasis. He stated that such a reflex, possibly vagal, may act in one or more of three ways: It may produce a change in vasomotor control which results in an excess of bronchial secretion; it may cause bronchial spasm, or it may lead to a swelling of the mucous membrane. However this may be, it is likely that traumatic collapse is rare as a cause of bronchiectasis because patients thus affected quickly recover completely or die. The rarity of collapse in cases of asthma is rather against this idea of Scott's, in any event.

Pleural inflammation and friction occur in cases of atelectasis, and caution must be observed in attributing the collapse to this cause.

Pleural effusions and pneumothorax, whether spontaneous or artificial, collapse the lung in a different way and are unlikely to cause immediate bronchial dilatation on account of the high pleural pressure they produce. Here, again, it must be recognized that pleural effusion and pneumothorax may both be secondary to atelectasis.[90] I met with an undoubted case of pleural effusion secondary to massive atelectasis,[67] though it is rarely possible to decide this question with any confidence in a particular case.

Collapse of the lung, due to fluid or air, is probably a rare cause of bronchiectasis, as complete reexpansion is the rule, even after three years, which is the usual duration of artificial pneumothorax. The rarity with which artificial collapse of the lung produces bronchiectasis is probably due to the absence of bronchial infection.

Certainly, reports of bronchiectasis following hydrothorax or pneumothorax are hard to find in the literature. Ballon, Singer and Graham [13] mentioned pleural effusion as a cause of bronchiectasis, but it did not occur in their own series of 149 cases. Farrell [41] and Findlay and Graham [29] recorded pleurisy as a cause in 2 cases, but did not mention effusion. A warning against accepting this alone as a cause of collapse has already been given. Failure of a compressed lung to reexpand or onset of infection during the period of compression could

88. Bradford, J. R.: Quart. J. Med. **12**:127, 1918.

89. Scott, W. J. M.: Postoperative Massive Collapse of the Lung, Arch. Surg. **10**:73 (Jan., pt. 1) 1925.

90. Burnham, A. C.: Surg., Gynec. & Obst. **19**:468, 1914. Escudero, L., and Adams, W. E.: Spontaneous Pneumothorax Associated with Massive Atelectasis: Experimental and Clinical Study, Arch. Int. Med. **63**:29 (Jan.) 1939.

lead to permanent bronchiectasis, but if either occurs it must be symptomless. It is therefore extremely unlikely that persistent collapse produces of itself permanent bronchiectasis, although an extensive bronchographic study would be required to clinch the matter.

Infection, and the consequent damage to the bronchial wall, seems to remain the deciding factor in the permanence of bronchial dilatation.

Empyema is mentioned in the literature as a cause of bronchiectasis in some instances, but it must be remembered that the lung in these cases is infected, and caution must be used in blaming the empyema itself.

Factors predisposing to atelectasis include partial bronchial obstruction and the various causes of inefficient aeration of the lung.

Partial bronchial obstruction obviously predisposes to collapse, because a complete bronchial block is much more likely to occur in a narrowed bronchial lumen. This is typically seen, in clinical experience, in those cases in which attention is drawn to the existence of a bronchial carcinoma by the occurrence of lobar or pulmonary collapse.

Chronic bronchial infection is a theoretic predisposing factor, but no direct evidence of its influence was found. Scott [80] found clinical evidence of preoperative bronchial infection in 6 out of 40 cases of postoperative atelectasis, but it does not appear that in these cases chronic infection existed. In an unpublished series of 53 cases of mine in which the patients were examined clinically and roentgenographically before and after abdominal operation, I found lobar or lobular collapse in 15 cases. In the 4 cases in that series in which preexisting bronchial infection could be diagnosed, however, there was no postoperative complication.

Inefficient aeration of a lobe or lung may be due to deficiencies of the respiratory apparatus or to faulty breathing.

Paralysis or inhibition of the diaphragm was proposed by Pasteur [91] as the sole cause of collapse of the lungs in most cases. He found that in 7 out of 8 patients who died with diphtheritic paralysis, partial or complete collapse of a lower lobe was present at autopsy. In 2 patients the collapse was bilateral. Later [92] he studied postoperative collapse and pointed out the severe inhibition of the diaphragm, which occurs particularly after operation on the upper part of the abdomen and which he considered as reflex. It is well known clinically that collapse occurs most frequently after operation in this region, a fact which supports his view. This theory is, however, largely discounted today in view of the clear evidence of infective obstruction presented by Jackson [6] and others who have been cited. It remains likely, however, that inefficient aeration of the lung, such as occurs when the diaphragm is inhibited,

91. Pasteur, W.: Lancet **2**:1351, 1908.
92. Pasteur, W.: Lancet **2**:1910, 1910; Brit. J. Surg. **1**:587, 1914.

will predispose to the occurrence of collapse. This fact was not denied by any author I was able to consult.

One might suppose that inhibition of costal breathing would also predispose to collapse if this is so, and dry pleurisy may, therefore, be mentioned as a possible, though unproved, predisposing factor.

Faulty breathing would appear to be another possible predisposing factor, though evidence of this, naturally, is absent. Thoracic breathing itself does not seem to act in this way. In the 15 cases of postoperative collapse which were just cited, I found that such collapse was as frequent in diaphragmatic breathers as in thoracic breathers. In fact, in 8 cases the patients were abdominal breathers and in 7 they were thoracic breathers.

2. *Causes of Parenchymal Damage or Destruction.*—The view that peribronchial destruction might cause dilatation of abnormal bronchi by weakening, in much the same way as collapse does, the normal support afforded to them by aerated lung tissue was previously expressed.

The causes of such damage or destruction are obvious. Bronchopneumonia, abscess and gangrene are examples, and the extensive peribronchial destruction that may occur in association with pneumokoniosis is another likely cause.

3. *Factors Favoring the Retention of Weighty Secretions within the Bronchi.*—Here, again, partial obstruction is the obvious cause, although the presence of severely damaged bronchi which have lost their tone altogether is itself a likely factor in the further retention of secretions.

As was already stated, the actual effect of the pressure of retained secretions is rather uncertain, but the possibility of its acting as a cause of abnormal bronchial strain cannot be ruled out.

CLINICAL FEATURES AND DIAGNOSIS

Much has been written on this subject, and the devotion of a section to it may, therefore, appear to be a work of supererogation. But in view of the relative, though perhaps decreasing, infrequency of the actual diagnosis, it was considered that a clinical review of the 68 cases was necessary.

The impression appears to be widespread and deeply rooted in the minds of the medical profession that bronchiectasis is something of a rarity. No statistical refutation of this idea is practicable, but that it is a complete, and most unfortunate, fallacy has been amply demonstrated by the large increase in the number of recognized cases since contrast roentgenography has been extensively applied to the study of bronchopulmonary disease. It is of interest to recall that this really extensive use of bronchography covers a period of not more than seven or eight

years, although the work of Sicard and Forestier [93] is now over eighteen years old. Before this, bronchiectasis could be diagnosed with certainty at autopsy only; in fact, comparatively few patients died in a hospital, since they were apt to be discharged as incurable after a period of medical treatment. Many persons no doubt died, as probably many still die, without admission to a hospital or observation by a physician. Furthermore, the clinical diagnosis, as has already been suggested, was largely a matter of presumption or suspicion. Thus, the period is, as yet, relatively short in which a new clinical conception of the disease could be formed.

In the present series of 68 cases, the average duration of symptoms before diagnosis was eleven years, and when one takes into account the average age of the patient, which was 17 years and 3 months, it is obvious that early diagnosis was not a feature. This duration appeared to be longer than that in other reported series, but since in the latter the average age was not given, comparison is unsatisfactory.

The patients were referred as possibly having tuberculosis or chronic bronchitis or with the comment "tuberculosis officer states that the patient is nontuberculous." Sixteen patients had spent longer or shorter periods in sanatoriums. Ochsner,[26] by the way, cited Hamilton as stating that 25 to 50 per cent of all inmates of tuberculosis sanatoriums are nontuberculous.

The following analysis of the present series of cases is therefore presented, without apology. No case has been met with in which persistent coughing, of varying severity, has not been an original symptom. In 39 cases (57 per cent) the cough dated from an acute illness of the respiratory tract, the details of which are to be seen in the accompanying tabulation.

Bronchopneumonia	22 cases	Primary 19; Measles 2; Pertussis 1
Lobar pneumonia	1 case	
Bronchitis	14 cases	Primary 7; Pertussis 4; Influenza 2; Rubella (?) 1
Aspiration of foreign bodies	2 cases	
Total	39 cases	

In 43 per cent of my cases the onset was insidious and could not be related to any definite cause. Warner [94] found 41 per cent in which the onset was insidious. Ballon, Singer and Graham [18] stated that bronchiectasis may be symptomless, and Fletcher,[48a] in a series of 100 cases, reported absence of cough in 32 per cent. Farrell,[41] however, found only 1

93. Sicard, J. A., and Forestier, J.: Bull. et mém. Soc. de chir. de Paris **46**:463, 1922.

94. Warner, W. P.: Factors Causing Bronchiectasis: Their Clinical Application to Diagnosis and Treatment, J. A. M. A. **105**:1666 (Nov. 23) 1935.

case out of 100 in which the presence of cough was not recorded, and Findlay and Graham,[29] 1 case only out of 25. Warner [94] and Rivière [95] appeared to regard coughing as a constant symptom. There is a certain discrepancy in these reports, but it is at least evident that coughing is an expected symptom. In 11 of my cases symptoms were said to have dated "from birth," and to have appeared insidiously, and in 12 cases the onset was during the first year. In 60 cases expectoration was an accompaniment of the cough, and in 40 of these the two commenced coincidentally. In 20 cases raising of sputum was first noticed at varying intervals after onset of the cough, and in 13 of these its appearance was "spontaneous." In the remaining 8 cases the bronchiectasis was apparently "dry," but in 1 case, that of an infant, large amounts of foul-smelling pus could be obtained by gastric lavage, and in another case, that of a boy of 10, copious expectoration followed bronchoscopic examination. In 2 other cases bronchoscopic examination revealed the presence of abundant pus in the bronchi, while in the other 4 cases bronchoscopic examination has not as yet been permitted. The observations in these 68 cases, therefore, do not make possible definite confirmation of the existence of "dry" bronchiectasis. It is perhaps significant that other reports of this condition are unconfirmed by bronchoscopic examination, as far as I have seen.[96] It seems possible that the number of cases of "dry" bronchiectasis might be materially reduced if a truly dry, or uninfected, bronchial system were made the criterion. It may be mentioned that expectoration was not always persistent and that "dry phases" were not infrequent. One may, perhaps, sum up the position fairly by saying that the clinical absence of sputum is perfectly compatible with a diagnosis of bronchiectasis, but is not proof that the bronchi in such a case are not heavily infected. Sputum was abundant, i. e., from 3 up to 20 ounces (85 to 565 Gm.) or more daily in 44 cases, and was definitely purulent in 41 of these. In 16 cases the amount was small or "moderate," i. e., less than 3 ounces (85 Gm.) daily, and was definitely purulent in 11. Sputum was fetid in only 18 cases, however, and it was evident that the mere duration of the period of expectoration was without influence in this respect, as the average duration in the 18 cases was six years only, as against an average of seven and one-half years for the 60 cases in which there was visible sputum. In only 2 cases did any change in the character of the sputum occur, and in neither could any obvious cause for this be elicited. In 1 case a mucous sputum became purulent after ten years, and in the other a purulent sputum became foul smelling after eighteen years. In all cases repeated examination failed to reveal the presence of tubercle

95. Rivière, C.: St. Barth. Hosp. Rep. **41**:123, 1905.

96. Wall, C., and Hoyle, J. C.: Brit. M. J. **1**:597, 1933. Burrell, R. S., and Traill, R.: Lancet **1**:182, 1930. Pinchin, A. J. S., and Morlock, H. V.: Brit. M. J. **2**:315, 1930. Moll.[65]

bacilli. Indeed, no characteristic bacteriologic picture could be demonstrated. In only 7 cases was a definite history of contact with tuberculosis obtained, and in 1 of these the patient had previously been treated in a sanatorium. At autopsy this patient was found to have an old tuberculous lesion at the apex, with tuberculous bronchopulmonary nodes pressing on the bronchus leading to the middle lobe. This pressure had evidently caused bronchial obstruction. The series, therefore, with 1 exception, did not appear to illustrate the etiologic role of tuberculosis, the importance of which seems to have been amply proved by Cohen and Higgins,[72] at Glen Lake Sanatorium, Oak Terrace, Minn., and by Vinson,[80] Bucher,[74] Andrews,[75] de Bruin[81] and others. As has been mentioned, however, it is mainly as a cause of bronchial obstruction that tuberculosis acts, and this action is difficult to exclude during life.

Hemoptysis of any severity was noted in only 7 cases (10.3 per cent), although a history of staining of the sputum was elicited in 8 others. This incidence is low as compared with that in certain other series, but particular inquiry was always made and it is certain that the record is a true one.

Thorpe[97] reported hemoptysis in 27 of 53 cases, and Acland[98] obtained a history of blood spitting in 12 of 25 cases and of staining of the sputum in 8 other cases. Ochsner[26] stated that hemoptysis occurred in 50 to 70 per cent of his cases, and Ballon, Singer and Graham[13] remarked that it "is more frequent in bronchiectasis than it is in tuberculosis." Farrell[41] and Fletcher,[45a] however, both gave lower values for the incidence of hemoptysis (42.8 and 6 per cent, respectively), Fletcher's figure being based on 100 cases. Warner[94] noted hemoptysis in 45 per cent of 110 cases and Hedblom in about 50 per cent of all cases.[24] It is likely that those authors whose work keeps them in close touch with cases of tuberculosis will meet with a greater number of instances of hemoptysis.

Wheezing, either persistent or occurring in asthmatoid attacks, was a prominent symptom in 10 cases (15 per cent). Three of these were first referred as cases of asthma, and the long-standing existence of cough and sputum was admitted only on inquiry. The symptom appears to have no importance except as a possible cause of diagnostic error, a mistake which should not occur. All 3 "asthmatic" patients gave a history of abundant purulent expectoration, and presented definite clubbing of the fingers and toes. It is, however, true that other authors appear to have been impressed by these asthmatic symptoms, for they mention asthma as a cause of bronchiectasis!

Except in the 10 cases just mentioned, breathlessness was not a feature, and in 50 of the remaining 58 cases the patients were able to

97. Thorpe, E. S., Jr.: Am. J. M. Sc. **177**:759, 1929.

98. Acland, T. D.: Practitioner **1**:379, 1902.

lead an active life. Eight patients were in poor general health and were forced to lead a semi-invalid existence. A history of nasal symptoms was elicited in 10 cases, though only on direct inquiry. In 8 of these, and in 5 others in which the patients denied any nasal trouble, sinusitis was found to exist. This is a lower incidence than certain authors have found, and it is not denied that sinusitis may have been overlooked in some cases. This matter is referred to in the section on etiology. The nasal symptoms were persistent "stopped nose" and intermittent nasal discharge.

A characteristic and not infrequent clinical feature of bronchiectasis is the recurrence of acute febrile exacerbations, in which symptoms and signs are temporarily increased. These illnesses are usually short lived, lasting for three or four days as a rule, but are severe and in many cases are referred to by the patient or his relatives as "pneumonia." Indeed, the appearance of the patient, who is often acutely ill and toxic, with high temperature and increased respiration and cyanosis, may closely simulate that of bronchopneumonia, and patches of tubular breathing and crackling crepitations are not infrequently noted. The short duration of the illness and the rapid recovery of the patient, who is rarely in bed for more than a week or ten days, put such a diagnosis out of count. Furthermore, the history of previous similar illnesses and of persistent symptoms in the intervals reveals the true nature of the complaint. Twenty-five cases of the 68, or 36.8 per cent, were typical instances of this syndrome. Fletcher [48a] reported recurrent febrile exacerbations in 28 per cent of his 100 cases, but other authors did not give definite figures.

In 39 cases, or 57.3 per cent, definite clubbing of the fingers and toes was present, though in varying degree. As the accompanying tabulation shows, clubbing was relatively more frequent in patients with purulent sputum and most frequent in those with fetid sputum. However, clubbing may be absent in a patient with fetid expectoration and may be present in another with only moderate mucous sputum or in one with no visible sputum whatever.

Incidence of Clubbing of the Fingers and Toes

	No. of Patients	No. with Clubbing
Purulent nonfetid bronchorrhea	38	20
Purulent fetid bronchorrhea	18	15
Mucous bronchorrhea	8	3
Absence of sputum (no bronchoscopic examination)	4	1

The mere duration of visible expectoration appeared to bear no relation to the incidence of clubbing. The average duration in the 39 cases in which digits were clubbed was seven and one-half years, which is exactly the average in the 60 cases in which there was visible sputum.

As has been stated, 60 of the 68 patients (88 per cent) had good general health. Twenty-eight patients, however, were definitely underweight, and most of those whose symptoms dated from infancy, i. e., 45 patients, or 66 per cent, were somewhat undersized.

Tonsillar infection was not a prominent feature. Six patients had suffered tonsillectomy, and 20 per cent of the remaining patients had some tonsillar infection. This was never gross, and the percentage cannot be considered significant in a group the majority of whom had been expectorating purulent or foul material for years. Such tonsillar infection as was present could not be shown to bear any relation either to the general health or to the severity of the symptoms.

Physical Signs.—Much is made in the literature of the frequency with which physical signs are absent or elusive in cases of bronchiectasis. The present series, although perhaps not large enough to furnish conclusive evidence, certainly gives no support to this view. Definite signs were completely absent in only 1 case, although in 1 other the only sign noted was local deficiency of expansion. Furthermore, physical signs, when present, were persistent, though varying in intensity from time to time.

Signs of which particular note was made were deficient expansion, impairment of the percussion note, abnormality of the breath sounds, presence of adventitious sounds and displacement of the cardiac apex beat. In no less than 63 of the 67 cases in which physical signs were detected, three or more of these five signs were noted.

Incidence of Local Signs in 67 Cases

Deficient expansion	54
Abnormal breath sounds	59
(Diminished 42, bronchial 17)	
Impairment of percussion note	56
(Impairment amounting to dulness, 20)	
Adventitious sounds: Crackling rales	56
Rhonchi	25
Displacement of the apex beat	21

In cases of atelectasis of the lower lobe of the lung, the sign not infrequently observed was impairment of the percussion note at the base of the lobe, which was most marked close to the spine and diminished as the axilla was approached. There were other signs limited to this area. The outline of the area of dulness or impairment in these cases was exactly the reverse of that so often noted in cases of pleural effusion.

In summing up the significance of these observations, it is justifiable to suggest that although the absence of physical signs by no means excludes bronchiectasis, it is in itself evidence against the presumptive diagnosis.

It is to be regretted that no record was kept of those cases in which a suggestive history led to the making of a bronchogram in the absence of physical signs. The number was not inconsiderable, however, and the consistently negative results were impressive. It is, of course, important that bronchiectasis should not be overlooked, particularly in children, in whom the prospect of successful treatment is so much brighter than in adults, and it is fully realized that negative bronchograms will continue to be inevitable. But, with care and discrimination in the assessment of the clinical and roentgenologic features in each case, it is felt that the number in which the patient is subjected to a bronchographic examination, with negative results, could be appreciably reduced. The risks of the procedure are slight, but with children a general anesthetic is always necessary, and I have met with 2 cases in which some anxiety was felt during the operation. In cases of unexplained hemoptysis and in cases in which there are suggestive clinical or roentgenologic signs, bronchographic examination is necessary, and no suggestion against it is intended. In the absence of such features, however, it is evident from this series that a history of an unexplained cough alone is an inadequate indication for bronchographic examination.

The sole case in the present series in which clinical signs were wholly lacking was one of unexplained hemoptysis in a young girl, and in her case the ordinary roentgenogram revealed a well marked irregular mottling of the basal region of the left lung, which extended far beyond the heart shadow. No case was observed in which definite clinical or roentgenologic evidence was absent before the use of contrast roentgenograms.

It is hoped that the impression has not been conveyed that the presence of physical signs is, in my opinion, diagnostic of bronchiectasis. As has been indicated, cases are met with in which a typical history and characteristic signs are associated with a normal bronchogram. Such cases, of course, require investigation, and, indeed, the patients should probably be reexamined at a later date, particularly if signs and symptoms persist. The evidence which was brought forward in the section on pathogenesis and pathology and the work of Roles and Todd on the "spread" of bronchiectasis give point to this suggestion.

The clinical study of a series of 68 cases of bronchiectasis has led to the conclusion that the disease is one which is usually associated with definite symptoms and physical signs and that any tendency toward indiscriminate bronchographic examination is to be deprecated.

Bronchiectasis in Infancy and Childhood.—In 29 of the 68 cases the patient was 12 years of age or under when first seen, and 3 of them were under the age of 2. In 2 of the infants under 2 years the roentgenologic changes were those described as characteristic of "congenital cystic disease of the lung," although the clinical features were not significantly

different from those in the other children. This diagnosis was, unfortunately, not verified by autopsy, as both these patients died at home. Whether or not these infants had, in reality, a congenital bronchial anomaly, theirs are the only cases of bronchiectasis in children which differ in any respect from the cases in adults. Further reference to congenital cystic disease and to bronchiectasis in childhood will be made when a classification of the cases is made, but it may be stated here that no evidence which in any way justifies the consideration of children suffering from bronchiectasis as a separate group was discovered from a careful study of the present series.

Sauerbruch [99] gave it as his opinion that in all cases of bronchiectasis in children in which the disease is confined to one lobe the condition is congenital in origin, and so-called congenital cystic disease of the lung has been reported as occurring rather more frequently in children.[35b] Furthermore, a number of authors reported series of cases of bronchiectasis in childhood, among them Boyd,[100] Anspach,[101] McNeil, MacGregor and Alexander,[22] Findlay and Graham [29] and Ellis.[102]

Such reports, although the authors did not state, and apparently had no intention of suggesting, that bronchiectasis in childhood should be studied apart from bronchiectasis in general, may yet create an impression to this effect. The study of the present series led me to conclude that there was nothing to be gained by the adoption of such an attitude, and it was for this reason that this section was written.

The real importance of discovering bronchiectasis in a child is the fact that treatment, especially surgical treatment, is so much more likely to be effective in the child and carries with it a much smaller risk.

ROENTGENOLOGIC FEATURES

Roentgenographic Survey of Present Series.—The preceding clinical summary has provided evidence of the importance of careful physical examination in the presumptive diagnosis of bronchiectasis. It is generally agreed, however, that physical examination alone is insufficient for the positive recognition of the disease. Roentgenographic and bronchographic examinations are essential for this purpose and for the further determination of the extent of the damage. It is therefore necessary to survey the roentgenologic observations in the 68 cases.

I did not find in the literature any statistical record of the roentgenographic features of this disease, except with regard to the frequency of

99. Sauerbruch (footnotes 17 and 39).

100. Boyd, G. L.: Canad. M. A. J. **25**:174, 1931.

101. Anspach, W. E.: Atelectasis and Bronchiectasis in Children: Study of Fifty Cases Presenting Triangular Shadow at Base of Lung, Am. J. Dis. Child. **47**:1011 (May) 1934.

102. Ellis, R.: Arch. Dis. Childhood **8**:25, 1935.

"atelectatic" shadows. General statements as to the changes which may be expected were, however, usual. Thus, it was said that the picture may be normal in a great many cases or that peribronchial "streakiness" alone may be seen. In certain cases more pronounced "scarring" was shown, occasionally with cavitation. In others, again, triangular, wedge-shaped shadows, which were usually basal but may be seen elsewhere, were reported. The frequency of these triangular shadows, which were shown by Comby [103] and Singer and Graham [104] to be due to local pulmonary collapse rather than to mediastinal effusions, has been variously estimated, but will be discussed later in this section. Finally, the heart was not infrequently seen to be displaced toward the diseased side.

All of these features were noted in the present series. Anteroposterior and, in the majority of cases, lateral views were taken, both before and after the injection of iodized poppy seed oil. The lateral view was helpful in many cases in determining or confirming the exact situation and extent of the lesion and is probably advisable as a routine. It is particularly in the diagnosis of bronchial dilatation in the middle lobe of the right lung and in the lingula of the upper lobe of the left lung (that portion aerated by the lower branch of the bronchus serving the upper lobe) that the lateral view is of value.

The following tabulation summarizes the observations in the present series of 68 cases.

Pathologic Changes Seen Roentgenologically

Local "fibrosis" (well marked, irregular shadowing)	30
Atelectasis (triangular shadow)	27
Cystic appearance (definite multiple cavities)	3
General opacity (massive collapse, with appearance of cavities)	2
No obvious abnormality, or mere "streaky" bronchial shadows	6
	68

There are two striking features in this tabulation. The first is the small number of normal roentgenograms, and the second is the large number of atelectatic shadows noted.

It is generally stated that a normal roentgenologic appearance is common in cases of bronchiectasis, although exact figures are not given.[105] Farrell,[41] however, reported roentgenographic changes in all of 100 cases. Warner [94] found only 17 instances of atelectasis in 110 cases, and Fletcher, only 20 in 100 cases. The diagnosis in my series was, however, definitely confirmed by bronchographic examination in 62 cases. Here, again, however, it must be stated that "fibrotic" mottling is not infrequently seen in cases in which no bronchial dilatation can be demon-

103. Comby: Bull. Soc. de pédiat. de Paris **23**:385, 1925.
104. Singer, J. J., and Graham, E. A.: J. Missouri M. A. **19**:390, 1922.
105. Hedblom.[26] Singer and Graham.[104]

strated. Bronchograms were accepted as the final diagnostic criterion in my series, although it now seems possible that in the future tomographic examination will also play a part. Davidson [106] showed me a beautiful demonstration of bronchial dilatation by this means, and Kerley [107] claimed to be able to diagnose bronchiectasis roentgenographically in many cases. Little difference in the result was observed by different methods, though better definition was perhaps obtained when the patient was under general anesthesia, which was employed in all cases of children. Iodized poppyseed oil was injected through the endotracheal tube in such cases. The other methods used were injection through the cricothyroid membrane and introduction by means of a nasal catheter.

In 3 cases of young infants, all of which were instances of gross cystic changes in the lung, bronchographic examination was considered inadvisable, but the roentgenograms were highly characteristic and the diagnosis was thought to be justified.

No attempt was made to classify the cases according to the shape of the bronchial dilatations as outlined by iodized poppyseed oil, though all the varieties described in the literature were seen. No etiologic or pathologic basis has been demonstrated to justify such a classification. In general, it appeared that a saccular appearance was perhaps associated more particularly with advanced disease, but as the treatment of any given patient was based more on the clinical condition and the bronchoscopic evidence than on the morphologic character of the bronchi, it appeared that nothing was to be gained from any such classification.

In 62 of the 65 cases in which bronchograms were made the diagnosis was immediately apparent. In 2 cases the diagnosis was disputed, even after repeated bronchograms were made, but was confirmed by subsequent operation and pathologic study. In the remaining case the diagnosis was based on the close similarity of the roentgenographic picture to that in the other 2 cases. The exact extent of the disease was not so readily determined, however, and it is possible that several mistakes were made.

Doubt and difficulty arose in several cases as to the involvement of the lingula of the upper lobe of the left lung and of the middle lobe of the right lung. Many thoracic surgeons hold that when the lower lobe of the left lung is involved the lingula is usually diseased also. In my series the lingula was clearly recognized as diseased in association with the lower lobe of the left lung in only 10 cases, whereas in 25 cases the lower lobe of the left lung appeared to be diseased but not the lingula. In 3 of these 35 cases bronchographic examination subsequent to operation revealed changes in the lingula, and in 19 the lingula was normal. In 13 cases no operation has as yet been performed. No case of apparent

106. Davidson, S. W.: Personal communication to the author.

107. Kerley, P.: Brit. J. Radiol. 5:234, 1932.

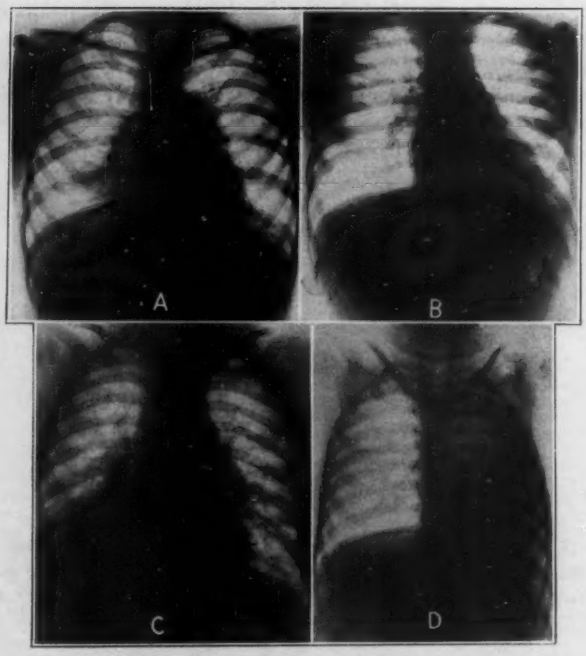

Fig. 16.—*A*, "fibrotic" mottling at the bases of both lungs. *B*, atelectatic appearance of the lungs. Note the dense triangular shadow within the heart shadow. *C*, cystic appearance of the lungs. Note the multiple cavities throughout the lower zones of both lungs. *D*, general opacity of the left pulmonary field. Note the displacement of the heart and trachea to the left.

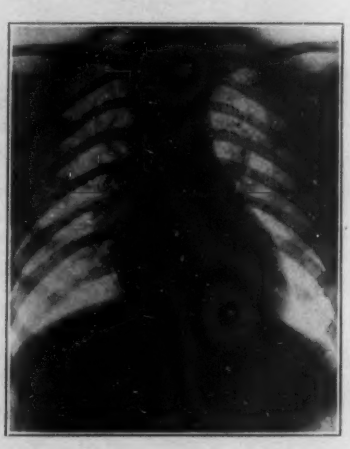

Fig. 17.—Normal appearance of the lungs and bronchi.

error with regard to the diagnosis of involvement of the middle lobe of the right lung has yet been demonstrated in this way, although doubt sometimes existed.

The possibility that dilatation was in fact not present at the first examination, but developed later, consequent to physical changes within

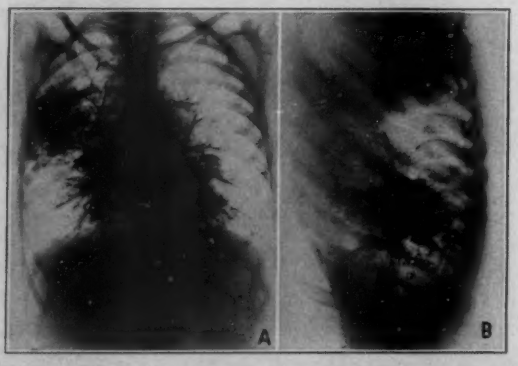

Fig. 18.—*A*, bronchogram in a case in which the diagnosis of bronchiectasis was in dispute for some time, but was confirmed by examination of the excised lung. *B*, bronchogram taken in the lateral view (same case). Note the evidence of lingular dilatations.

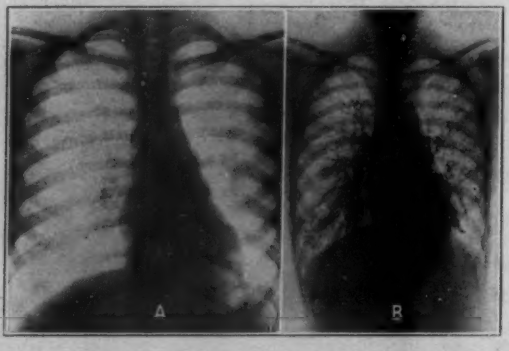

Fig. 19.—*A*, an atelectatic shadow. *B*, the lower lobe and the lingula of the left lung are involved. The bronchi of the lower lobe are crowded within an atelectatic shadow. The lingula, even though the bronchi are crowded, casts no shadow.

the thorax produced by the operation, must be borne in mind. The conclusion arrived at in the section on pathogenesis regarding diseased bronchi potentially liable to dilatation and the work of Roles and Todd [108]

108. Roles, F. C., and Todd, G. S.: Brit. M. J. **2**:639, 1933.

on the "spread" of bronchiectasis lend point to this suggestion. No proof, however, can be offered.

Experience with these doubts and difficulties leads to the conclusion that the taking of both anteroposterior and lateral roentgenograms of each lung separately is necessary in each case, and latterly this has been done. But in the majority of cases ignorance of the necessity of this practice, and certain other causes, prevented its adoption. One hindrance to the general adoption of unilateral bronchographic examination is likely to be the large number of such procedures performed, which is a further argument in favor of their reduction when not indicated.

In 1 case, the lingula alone showed definite dilatations, and that in the lateral view only. The bronchi leading to the lower lobe were apparently

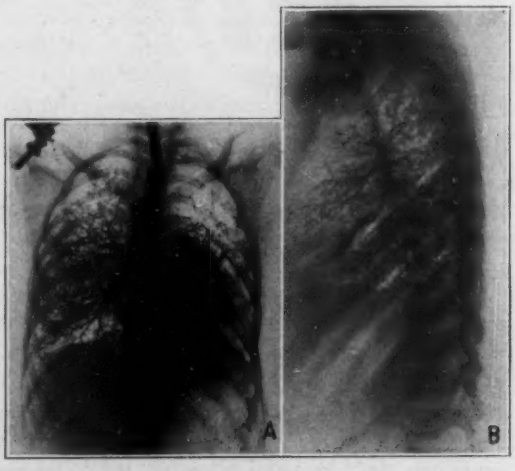

Fig. 20.—*A*, a case in which the anteroposterior view showed no clear evidence of dilatation. *B*, dilatation of the lingular branches, as seen in the lateral view. (Later, the bronchi of the lower lobe became obviously dilated.)

normal, but dilatations were demonstrated later, and the lobe was removed at a second operation.

One further technical point may be mentioned. Ochsner [26] claimed to have demonstrated dilatations in cases in which the alveoli rapidly became filled with iodized poppyseed oil, obscuring the bronchi. He urged injection of iodized oil under the fluoroscopic screen, stating that within a few minutes the bronchi may be obscured and bronchiectasis missed. This difficulty was not serious in any case in my series, and the matter has not been mentioned by other authors. In 1 case the bronchi were observed in the anteroposterior view, but were clearly shown in the lateral view. The danger of error can be eliminated by avoiding the use

of too much iodized oil. When the normal maximum dose of 20 to 30 cc. (5 to 10 cc. for children) is used, it is seen that a characteristic feature of bronchiectasis is the failure of the iodized oil to enter the alveoli at all in the diseased area, whereas it enters readily when the bronchi are normal.[109] Personally, I regard a bronchogram with suspicion, even if the bronchial caliber appears roughly normal, when the alveoli are not entered.

Apparent Situation and Extent of Bronchiectasis in the 65 Cases in Which Bronchograms Were Made

Unilateral	53	Left	37
		Right	16
Bilateral	12		
Unilobar	38	Lower lobe, left lung	25
		Lower lobe, right lung	11
		Middle lobe, right lung	1
		Upper lobe, right lung	1
Multilobar	27	2 lobes affected	22
		3 lobes affected	5

The features to which especial attention may be drawn are the following: the preponderance of left-sided disease in instances of unilateral disease, which accords with general experience; the relative frequency of multilobar disease, and the fact that only 1 case of apical bronchiectasis was met with. Apical bronchiectasis is liable to occur particularly in cases of tuberculosis, and the fact that proved tuberculosis was present in only 1 case in my series (one of bronchiectasis of a middle lobe) may account for the low incidence of apical bronchiectasis.

The conclusions which may be drawn from this roentgenologic survey seem to be as follows:

1. Bronchograms are readily diagnostic in the great majority of cases, but if doubt exists, particularly if the iodized oil fails to enter the alveoli, reexamination is indicated. If doubt still exists, the case must be reconsidered as a whole before bronchiectasis is excluded.

2. The determination of the extent of the disease may be difficult, but is likely to be materially assisted by unilateral bronchographic examination of the lungs. Lateral views are valuable.

3. The proportion of normal roentgenograms was somewhat lower than that in other reported series.

Atelectatic Bronchiectasis: Roentgenologic Diagnosis.—This subject requires especial note, both because of its great prominence in the present series and because of recent theories, previously mentioned, of the role of collapse in the production of bronchiectasis. In the section on classification atelectatic bronchiectasis will be treated as a whole. Here it is intended merely to discuss the roentgenologic criteria of its diagnosis.

109. (*a*) Warner, W. P.: Canad. M. A. J. **27**:589, 1932. (*b*) Findlay and Graham.[29]

Roentgenologically, the atelectatic lobe typically appears as a dense homogeneous shadow, having the shape of a right-angled triangle, with the base on the diaphragm and the long side directed laterally and upward. Medially, the triangle merges with the heart shadow on the right side, and on the left side the whole shadow usually lies within the heart shadow, and some care is necessary to distinguish it. This description applies to the anteroposterior view of atelectasis of the lower lobe involvement of the middle lobe of the right lung. In the lateral view the middle lobe of the right lung is seen as a triangular wedge with its base against the sternum, while the lower lobe of the right lung has its base against the diaphragm.[110] The shadow, in the lateral view, assumes a roughly rectangular shape if both the lower and the middle lobe are collapsed.

The lower lobe is much the most frequently involved, but in cases of tuberculosis or of bronchial carcinoma the upper lobe is frequently affected in this way. A triangular wedge then occupies the extreme apical region, with the base directed laterally.

Bronchographic examination demonstrates dilatation of the bronchi, which are crowded together within the dense shadow of the collapsed lobe. The lobe, which can thus be compared with that of the other side, is seen to be greatly shrunken, and the bronchi of the remaining lobe or lobes are observed to occupy the rest of the pulmonary field.

The heart may be displaced toward the affected side in cases of unilateral disease, but this is not universal; indeed, it was noted in only 8 of the 23 such cases in this series. Compensatory emphysema or fixation of the mediastinum appeared to be the reason for the absence of displacement of the heart in the others.

In cases of massive pulmonary atelectasis there is evident on the diseased side a general opacity, which is homogeneous, although cavities may be seen within it occasionally, as in 1 case in this series. The heart is displaced. Two cases illustrated this phenomenon, which has been fully described by Warner.[109a] It is now necessary to consider whether the present accepted roentgenologic criteria of atelectasis require any extension or modification.[111] It will perhaps have been noticed that cardiac displacement was observed in 11 cases in which the recognized requirements for the diagnosis of atelectasis were not satisfied. A study of these cases showed that in 10 the roentgenographic appearance was that of "fibrosis." In the other case the roentgenogram was completely normal. The bronchogram in all cases revealed dilatation and some crowding. Furthermore, in a case of atelectatic bronchiectasis of the lower lobe of the left lung, the lingula of the upper lobe was also affected, although outside the triangular shadow. Lander [111] showed me the roentgenograms in a case of hemoptysis of unknown origin. In the

110. Gill, A. M., and Pearson, J. E. G.: Arch. Dis. Childhood **2**:87, 1936.
111. Lander, F. P. L.: Personal communication to the author.

roentgenogram no abnormality was to be seen, but the bronchogram revealed gross dilatation and crowding of the bronchial tubes leading to the upper lobe of the right lung, so that they occupied a definitely smaller area than the normal. The bronchi of the middle and lower lobes occupied the remainder of the pulmonary field. Here was an instance of a shrunken lobe, containing crowded, dilated bronchi, which yet cast no shadow in the roentgenogram.

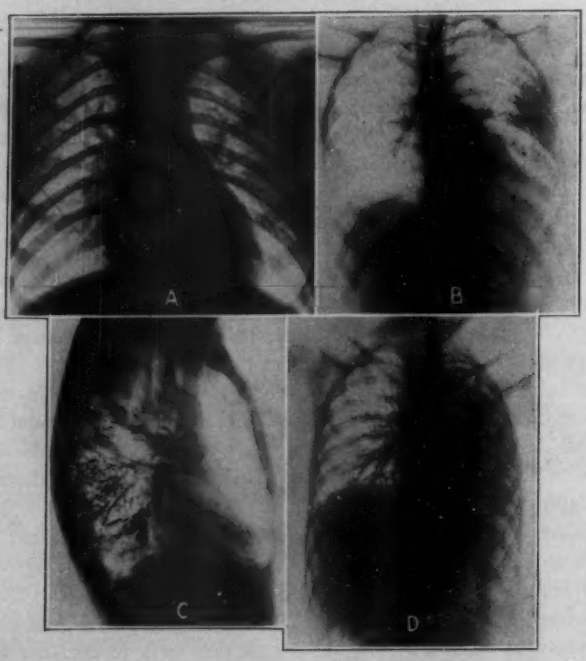

Fig. 21.—*A*, normal appearance of the lungs. No atelectatic shadow is visible. *B*, atelectatic bronchiectasis. Note the restriction of dilatations to the lower lobe and the crowding of the bronchi. *C*, lateral view (from same case as that from which *B* was taken). Note that the rest of the pulmonary field is occupied by the expanded upper lobe. There is a slight suggestion of dilatation of a lingular branch. *D*, massive atelectatic bronchiectasis.

The possibility is suggested that bronchiectasis may occur in lobular areas of collapse which are of insufficient size and density to produce a homogeneous shadow, or even in some cases to produce a shadow at all.

Mason [112] informed me that it is not infrequent at operation to recognize in the unhandled bronchiectatic lobe firm, purple patches, an observation which lends support to my suggestion.

112. Mason, G. A.: Personal communication to the author.

More evidence is required before this idea can be accepted, but it is put forward here as worthy of consideration and further investigation. If it were shown to be correct, it would certainly increase the importance to be ascribed to the role of pulmonary collapse in the production of bronchiectasis.

Bronchoscopy.—I did not perform the bronchoscopic examination in this series, but the results of others have tended to show that this procedure is of value as a guide to the surgeon in his decision whether to operate rather than as a diagnostic aid. The value of bronchoscopy in the treatment of bronchiectasis is not now seriously considered, except in cases of relatively recent atelectasis. Only a negligible amount of secretion can be aspirated in this way as compared with the copious amounts obtained in cases of massive atelectatic bronchiectasis by postural coughing and breathing exercises.

The case of the patient referred to in the section on pathogenesis (page 417) illustrates this point. Postural drainage and breathing exercises were instituted and produced definite improvement in the physical signs, with partial return of the heart's apex toward its normal position. Bronchoscopic examination was then performed and a small amount of tenacious mucopurulent material aspirated. This examination was followed by the introduction of iodized oil, which revealed a normal bronchial tree. The physical signs indicated a return to normal conditions. Jackson [70a] emphasized the value of bronchoscopy in the treatment of such condition and his opinion is to be respected. In the case reported here, however, it seems that postural coughing and adequate physical exercises went far toward producing a cure before a bronchoscopic examination was carried out.

CLASSIFICATION

The classification of bronchiectasis is not a simple problem, and its solution has not been advanced by the development of a wide literature, owing to the absence of correlation of the clinical and roentgenologic findings with the morbid anatomic changes.

Reasons for doubting the value of any classification based on the morphology of the affected bronchi as shown in the bronchogram have been given in the preceding section. The conclusion was reached that the morbid anatomic appearance in the 28 cases in which material was available provided the only sound basis for classification.

The complete records of the patients in these cases were then examined again, and the excised lobes divided into two groups according to the morbid microscopic anatomy, as already described in the section on pathogenesis.

A detailed analysis of all the recorded observations in both the atelectatic and the bronchopneumonic group was made, and it appeared that the only satisfactory criterion for a classification was the bronchogram.

In the atelectatic group definite crowding of the affected bronchi was noted, and the lobe or lobes concerned were seen to occupy a much smaller part of the pulmonary field than normal. The unaffected lobe or lobes were observed to be expanded, apparently in order to compensate

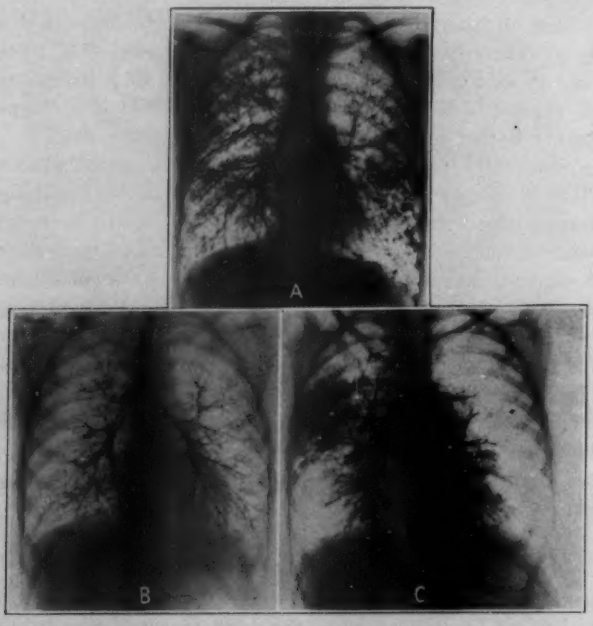

Fig. 22.—*A*, a bronchogram in which cylindric dilatations are visible at the base of the left lung. The bronchi of the lower lobe are crowded, and the upper lobe occupies by far the greater part of the pulmonary field. *B*, a bronchogram showing a normal bronchial tree. *C*, a bronchogram in a case of atelectatic bronchiectasis in which bronchial crowding was absent.

for this shrinkage. In 11 of the 18 cases of the atelectatic form there was neither cardiac displacement nor contraction of the chest wall, which shows how complete this compensatory expansion may be.

In the bronchopneumonic, or, better, the bronchogenic, group, on the other hand, there was no evidence of crowding of affected bronchi, and no abnormal bronchial distribution was present.

In 1 case only out of the 28 did this method of classification appear to fail.

In this case, that of a girl of 4, the lower lobe of the left lung was removed at operation and was found to be the seat of extensive collapse and of pronounced bronchial and peribronchial destructive change.

The lobe was also definitely, though moderately, shrunken. The roentgenogram showed fibrotic mottling, and the bronchogram, although it revealed moderate cylindric dilatations, was free of any evidence of crowding or of abnormal bronchial distribution. It is obvious that without examination of the actual lobe this case would have been classified under the bronchopneumonic type, and it must be admitted that this error is likely to occur occasionally. The reverse error, however, is unlikely to occur, and it is not considered that this exceptional case invalidates the proposed method of classification. Doubt and difficulty arise from time to time in the diagnosis of bronchial dilatation by bronchographic examination, but this is not held to destroy the value of the contrast roentgenogram in the diagnosis of bronchopulmonary disease.

It is likely that cases will occur which should be placed in a "combined" group. That is to say, a patient may have atelectatic bronchiectasis in one lobe and a bronchopneumonic type of change in another. The classification is really one of lobes rather than of cases.

Finally, reference must be made to a case reported by Sparks.[113] It was that of a patient of 22 who was found to have a triangular shadow at the base of the left lung. The right lung was injected with iodized poppyseed oil, and the bronchi were found to be normal, but it was noticed that the triangular shadow had disappeared. The left lung was then injected, and well marked bronchial dilatations were shown at the base, although the atelectatic shadow was no longer present. This case was cited as proof that atelectasis may be an incident in the course of previously established bronchiectasis. The possibility that this occurs is in no way disputed here, but the absence of bronchographic evidence of a "preatelectatic" state in Sparks's case detracts from its value as a proof. The frequency of collapse in established bronchiectasis, if it occurs, cannot be estimated, but as no undoubted case has been reported, as far as is known, it is unlikely to be of serious significance. What is more likely is that reexpansion or partial reexpansion of an atelectatic lobe occurs, but that bronchial damage has already insured the permanency of the dilatations, which, therefore, do not disappear.

Such a case occurred in the present series, and is illustrated.

The remaining 40 cases were then considered. Two of these were set apart as instances of "congenital cystic disease of the lung," (see section on pathogenesis), leaving 38 cases to be classified.

113. Sparks, J. V.: Brit. J. Radiol. **4**:30, 1931.

These 38 cases were grouped according to the bronchographic changes, as has just been described. The final analysis of all 68 cases was, then, as follows:

Atelectatic bronchiectasis (1 case classified on morbid anatomic basis)	42	(61.8 per cent)
Bronchogenic (or bronchopneumonic) bronchiectasis	24	(35.2 per cent)
"Combined" forms	0	
Congenital cystic disease	2	(3 per cent)

The high incidence of the atelectatic type will be noted.

This simple classification of bronchiectasis, apart from its general convenience, is likely to be of value chiefly as a guide to prognosis and treatment. The classification submitted here is capable of acting as a basis for that exclusive and detailed study of the prognosis of bronchiectasis as a whole which has not yet been made, but which is so urgently required.

As regards treatment, the decision for or against operation and as to the best time if operation seems advisable is of vital importance in each case. Many aspects of the case must be considered before the final decision is reached, but perhaps the most important of these is the prospect of cure or satisfactory improvement if nonsurgical measures are undertaken. It is in this connection that the present classification is likely to be helpful.

The occurrence of temporary bronchiectasis was referred to in the section on pathogenesis, and it will be remembered that only in cases of atelectasis was this temporary condition reported. Now, although in the majority of the atelectatic lobes in the present series the bronchi were found to be seriously damaged, there were several in which such damage was relatively slight. Furthermore, the average duration of disease in the 42 cases of atelectatic type, before diagnosis, was seven years and four months. This is less than half that in the cases of bronchogenic type, but is nevertheless considerable. With earlier diagnosis, it seems probable that the percentage of cases in which restoration to normal is possible would be greatly increased. In a case of atelectatic bronchiectasis of recent onset or in one in which infection is moderate, active nonsurgical treatment by adequate postural drainage, breathing exercises and the bronchoscopic method, if necessary, together with any other indicated measures, such as the removal of chronic sinal infection, should be given full trial before surgical intervention is even considered. In a case of bronchogenic type, on the other hand, permanent success with medical treatment is much less likely, and the decision rests rather on the degree of bronchial infection, the general condition of the patient and the presence or absence of suppurative sinusitis. It is considered likely that in most of these cases operation will eventually be required if a cure is

desired and that this should not be postponed beyond the age of childhood unless bronchial infection is slight.

It is proposed to conclude this section with a brief general account of the two groups which were set up, the atelectatic and the bronchogenic. The etiologic factors in the two groups did not differ significantly, although bronchitis, primary and secondary, was much more frequent as a causal factor in the atelectatic group (29 against 16 per

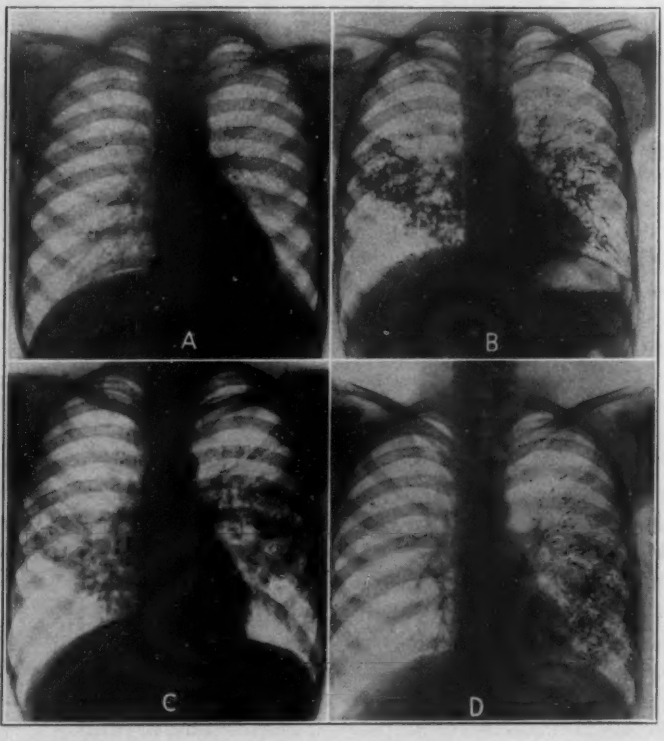

Fig. 23.—This case of atelectatic bronchiectasis was one in which disappearance of the triangular shadow was not accompanied by disappearance of the dilatations. *A*, original roentgenogram. Note the shadow at the base of the left lung. *B*, original bronchogram. Note the dilatations crowded within the triangular shadow. *C*, second roentgenogram. Note the absence of a triangular shadow. *D*, second bronchogram. Note the persistence of the bronchial dilatations and the slight change in their relative positions.

cent). No conclusion with regard to infection of the upper respiratory tract could be reached, owing to the small number of cases in which sinusitis was discovered. A "spontaneous" onset was equally common in the two groups (39 and 44 per cent). Clinically, a much higher incidence

of those recurrent febrile exacerbations which have been referred to as "chest attacks" was found in the atelectatic group (31 against 4.4 per cent). It seemed probable that this increase was due to recurrent "retention" bronchiolitis or so-called pneumonitis, which would more readily occur in a collapsed lobe. A much stricter localization of clinical signs was also noticed in cases of the atelectatic group. Physical signs were confined to the basal region near the spine in 38 out of 42 cases, and in 3 others in which axillary signs were present subsequent investigation revealed infection of the lingula or middle lobe of the right lung. It was true that this strict localization of signs did not always correspond with the extent of the disease, which was sometimes greater than the signs suggested. However, since this localization of physical signs was present in only 1 out of 24 cases of the bronchogenic type, it was a helpful differentiating point. In the other 21 cases of the bronchogenic form with adequate signs these were widespread over the base and in the lower part of the axilla, in spite of the fact that only one lobe was affected on either side in the great majority of instances. In 2 cases of bronchogenic type physical signs were slight or absent. Otherwise, the clinical manifestations in the two groups were almost identical, including clubbing of the digits (63 and 64 per cent). The general health was the same in the two groups.

The ordinary roentgenograms, however, showed some striking differences, although these were of doubtful value in differential diagnosis. "Fibrotic" shadows were more frequently met with in the bronchogenic group (50 against 78.3 per cent), and triangular shadows were found only in the atelectatic group. They were present in 40.5 per cent of cases, and "fibrotic" shadows were actually more frequently seen in cases of the atelectatic form than were the typical triangular shadows. This lends emphasis to the suggestion of Lander, which was discussed in the section on the roentgenologic features, that the criteria of collapse required extension, or at least reconsideration. It may be that the crowding and abnormal distribution of the bronchi, which were used as a criterion in this essay, will supply this need, at least in part.

A summary of the salient features of each of the two main groups, as noted in the present series, is given in the following tabulation.

Features	Comment
Etiologic	Bronchitis was nearly twice as common in the atelectatic group.
Clinical	Febrile "chest attacks" were seven times as frequent in the atelectatic group.
	Strict localization of physical signs was usual in cases of atelectatic bronchiectasis, but infrequent in those of the bronchogenic type.

Features	Comment
Roentgenographic	"Fibrotic" shadowing was much more commonly seen in the bronchogenic group. Triangular shadows were met with only in cases of the atelectatic type, but were seen in only 40 per cent of these.
Bronchographic	Crowding of affected bronchi was the rule in atelectatic bronchiectasis, though 1 exception was noted. Crowding of affected bronchi was not seen in a case of the bronchogenic type.

PROGNOSIS AND DEATH

Factors in Prognosis.—Any discussion of the prognosis of bronchiectasis almost inevitably recalls Laennec's famous patient,[25] an unmarried woman of 82. She steadily followed her occupation as *maitresse de piano,* although she had suffered from a persistent cough with purulent sputum since the age of 16. Laennec saw her a short time before her death, and at autopsy found a gross degree of bronchiectasis affecting all three lobes of the right lung and the upper lobe of the left lung!

Such cases of long standing, in which symptoms are compatible with fairly good health and ability to work normally, are commonly met with. On the other hand, all physicians are familiar with patients who succumb to one or another complication after a year or so.

This extreme variability in the outlook precludes any general estimate of prognosis, and a detailed study of an extensive series of groups of cases in now overdue.

What is required is information which will enable the physician to make a reasonable and reasoned estimate of the prospects in the individual case. The value of this is evident when the question of surgical intervention arises, as it now does in the majority of cases. The physician is naturally loath to advise an operation, which is still a serious risk to the patient, in a case in which good general health and a comparatively normal life are possible, unless he can feel confident that operation will greatly prolong life and permanently relieve or abolish symptoms.

Experience and "clinical instinct" are repeatedly set at naught by the vagaries of chronic bronchiectasis. The factors which affect the prognosis or the extent to which they do so is not known with any certainty.

Which patients are good surgical risks, and which are bad ones? Is fetid expectoration a bad prognostic sign? What is the significance, if any, of clubbing of the digits? Does the coexistence of suppurative sinusitis reduce the expectancy for life, and to what extent? Are there any other etiologic or clinical features which are of value in this respect? These are a few of the questions which await an answer.

The literature which was consulted did not greatly help to elucidate these problems, because general statements of mortality after an average period of observation give no guidance in the individual case.

In a recent article, Cookson and Mason [114] were emphatic as to the risks to which the bronchiectatic patient is exposed if there is no surgical intervention. They reported a series of striking instances of sudden and fatal complications occurring in patients who were awaiting operation. They concluded that bronchiectasis is a fatal disease and that operation offers the main hope of cure or prolonged life.

Here, again, however, one is faced with the problem of the selection of the right case for operation, knowing, as one does, the possible duration of good health and general activity in some established cases. One of the patients in the present series is now well and free of cough and sputum after expectorating fetid material for fifty years, and Ballon, Singer and Graham [18] stated that in some cases bronchiectasis may become dry! The analysis of the 68 cases which now follows cannot supply an answer to the problem, in view of the small number and the short period of observation (less than six years). It is submitted, however, as an indication of the *kind* of information which I believe is required. It may, in addition, have some suggestive value.

Analysis of Sixty-Eight Cases of Bronchiectasis from the Standpoint of Prognosis

Present Condition

Fifteen are known to be dead, 6 of whom died after operation.
Four are known to be in poor health, 2 of them after operation.
Twenty-five are known to be well and symptom free, 16 of them after operation.
Nineteen are known to be *in status quo*, 6 of them after operation.
The present condition of 5 is unknown.

Fetid Expectoration

	Total Number	Number Dead	Percentage Dead	Number Operated On	Postoperative Mortality, Percentage
Patients with fetid sputum	18	6	33.4	13	33.6
Patients without fetid sputum	50	9	18	23	13.0

Clubbing of the Digits

	Total Number	Number Dead	Percentage Dead	Number Operated On	Postoperative Mortality, Percentage
Patients with clubbing	42	11	26.2	25	24.0
Patients without clubbing	26	4	15.4	11	18.2

Atelectatic and Bronchogenic Groups

	Total Number	Number Dead	Percentage Dead	Number Operated On	Postoperative Mortality, Percentage
Atelectatic group	42	12	28.6	23	30.4
Bronchogenic group	24	3	12.5	13	7.7

Etiologic Factors Other Than Sinusitis

	Total Number	Number Dead	Percentage Dead
Pneumonia	23	8	34.8
Bronchitis	14	5	35.4
"Spontaneous" occurrence	29	2	7.1

114. Cookson, H. A., and Mason, G. A.: Edinburgh M. J. **45**:844. 1938.

It was emphasized that these figures can have no more than suggestive value. Such as they are, however, they seem to indicate that fetid expectoration is an unfavorable prognostic sign, the mortality being almost double that among patients without fetid expectoration, and also that patients with this condition are less favorable operative risks. Clubbing of the digits seems a less valuable criterion, although the figures tend in the same direction.

Perhaps the most striking results are to be seen in the comparison of the two groups (the atelectatic and the bronchogenic). The mortality in the atelectatic group is more than twice, and the operative mortality nearly four times, that in the bronchogenic group. The operative risks must be balanced carefully against the prognosis for medical treatment in any study of the question.

Etiologically, the cases were classified into general groups in order to avoid absurdly small numbers. It is interesting to observe the low death rate in the group with "spontaneous" origin—only one-fifth that in the other groups.

It is not proposed to speculate on the causes of these apparent factors in prognosis. When statistically convincing information is at hand, it will be time enough for an investigation of the why and the wherefore.

It may be stated that the duration of symptoms did not appear to have any bearing on the prognosis. For the 15 patients who died, 8 of them after operation, the average duration was eleven and two-tenths years, exactly that for the whole 68 patients.

The factor of age must next be mentioned. It is particularly with reference to the results of operation that the question of age assumes importance. The average age of the 28 patients who survived operation was 15.6 years, and the average of the 8 who died soon after operation was 20.4 years. These averages were exactly the same as the corresponding figures for the whole series, but of the 13 children aged 12 and under at the time of operation only 1 died, whereas of the 23 patients aged 13 or over, 7 died after operation. These figures are small, but represent a mortality of 7.7 per cent, as against one of 30.8 per cent. Figures, however, do not illustrate the position adequately. The remarkably rapid and uneventful postoperative course of lobectomy in children is repeatedly observed and is in marked contrast to the prolonged, uncertain and anxious period of recovery in older persons. The only certainty with regard to operative prognosis at present is that the risk rises rapidly with age once childhood is left behind.

Although they may maintain a good standard of general health for many years, patients with bronchiectasis have a reduced resistance to infection and are unlikely to regain their health when once it has broken down. This fact was observed in patients whose cases were included in

the present series and is, I think, generally accepted. Of 9 patients who were in poor health when first seen, only 3 are now alive, and all of these are bedridden.

There is one other prognostic sign of certain value, and that is persistent albuminuria. Bronchiectatic patients with persistent albuminuria are not likely to live long and are likely to collapse if the slightest surgical intervention, even bronchoscopic examination, is attempted.[115] It is generally held that persistent albuminuria, apart, of course, from complicating nephritis, is an indication of the development of amyloid disease.

Bronchiectasis which is secondary to fatal conditions, such as bronchial carcinoma or aortic aneurysm, has often no influence on the prognosis, but in some cases may hasten the end by the development of those complications which are more peculiar to itself and which are to be dealt with later in this section.

Fatal Complications.—Certain of the nonfatal complications have already been mentioned in the course of this essay. The course of the disease tends to undergo no dramatic changes until the final breakdown occurs. Febrile exacerbations, which were referred to under the name of "chest attacks," are liable to occur and to recur from time to time in certain cases. Sinusitis is frequent, but is usually symptomless.[116]

It is now necessary to refer to those more serious complications which herald, if they do not immediately bring about, a fatal termination of the disease.

These may be classified into three groups:

A. Complications related to local exacerbation or to direct spread of infection within the lungs or thoracic cavity.

B. Complications which are a direct result of associated conditions or intercurrent disease.

C. Dissemination of infection by the blood stream and the late results of chronic sepsis.

A. Intrathoracic Complications: In certain cases of bronchiectasis a gradual increase in the symptoms, accompanied by an irregular, and probably a moderate, degree of fever, indicates an exacerbation of the disease. There is no acute onset, but a steady decline in the general health takes place, and although death does not occur for months, or perhaps a year or two, the general condition fails to improve and it is necessary to recognize that a limit to the life of the patient has been set. There were 7 cases in which the patients exhibited this gradual change in the general course of the disease. Five of the patients are now dead. The other 2 are still alive, but both are ill, febrile and emaciated.

115. Mason, G. A.: Personal communication to the author.

116. Walsh, T. W., and Meyer, O. O.: Coexistence of Bronchiectasis and Sinusitis, Arch. Int. Med. **61**:890 (June) 1938.

These 7 cases thus account for a third of the total deaths during the period of observation.

The cases in which there are febrile exacerbations, or "chest attacks," are readily differentiated from these cases of declining health. The onset is acute with high fever, the duration is short and the general health is rapidly regained. In fact, a child may be taken ill on Friday night and be at school on Monday. These acute attacks had no noticeable effect on the prognosis in the present series, and the case mortality was exactly the same as that for the whole series.

Acute fatal exacerbations do, however, frequently occur, whether as a terminal event in the type of case which has just been described, or as an abrupt complication in a case in which the patient has been previously well and active. They take the form either of local abscess or of gangrene, with or without resulting empyema or pyopneumothorax, or of aspiration pneumonia affecting a previously healthy lobe or lung. It is usually not possible to obtain evidence of any external infection as a determining factor in the occurrence of such a fatal complication, although one would think that this must be the cause in some cases.

In cases in which death occurs from postoperative infection, it is not uncommon to find suppurative pericarditis as the probable cause of death.[117] No evidence of pericarditis was found, however, in patients who died of the disease itself, without operation, at the Royal Victoria Infirmary over a ten year period.

Finally, some patients who suffer from bronchiectasis die of cardiac disease (see also section C). Cookson and Mason described a case in which I had an opportunity of seeing the patient, a young man of 25. He had had symptoms of bronchiectasis for six years, during which time foul expectoration had been persistent. For the greater part of the year prior to admission to the hospital his health had been steadily declining, and he was ill on admission. Two days later he became very ill, with high temperature, and auricular flutter developed, which persisted until death, ten days later.

Another patient who died of cardiac failure, in the Royal Victoria Infirmary, had suffered from cough and expectoration for many years. Autopsy revealed that he had extensive bronchiectasis, with much parenchymal scarring. The right side of the heart was greatly dilated, and it seems possible that death was due to increased resistance in the pulmonary circulation, although it remains uncertain whether this is to be ascribed directly to the bronchopulmonary condition.

This case was taken from the pathologic records of the Royal Victoria Infirmary, and was not included in the present series. Both Moll [65] and Jex-Blake [118] reported deaths from cardiac failure.

117. Mason, G. A.: Personal communication to the author.

118. Jex-Blake, A. J.: Brit. M. J. 1:591, 1920.

Finally, the occurrence of fatal hemoptysis, though not observed in the present series, was reported by several authors.[119]

B. Complications of Associated Conditions and Intercurrent Diseases: Bronchiectasis may be only an indirect cause of death, or the patient may die of intercurrent disease.

When bronchiectasis is due to carcinoma of the bronchus or to an aneurysm or is associated with tuberculosis, death is not infrequently due to the primary disease or its complications. No cases of such nature were included in the present series. In addition, associated sinusitis or otitis is not uncommon in cases of bronchiectasis, according to the literature, and it is likely that more instances of such association would

TABLE 1.—*Causes of Death in the 27 Cases of Bronchiectasis in Which Autopsy Was Performed at the Royal Victoria Infirmary, Newcastle-on-Tyne, 1929 to 1938*

A. Intrathoracic, direct	
Abscess and gangrene of the lung	7
Suppurative bronchopneumonia	7
Empyema (probably secondary to pulmonary abscess)	2
Lobar pneumonia (?)	1
Cardiac failure	1
Total	18
B. Associated conditions and intercurrent disease	
Intracranial abscess *	5
Flare-up of existing tuberculosis	1
Pneumococcic peritonitis	1
Portal pyemia	1
Total	8
C. Infection of the blood stream and the late results of chronic sepsis	
General pyemia	1

* Intracranial abscess was placed in group B, in view of recent evidence against the idea that its causative agent is blood borne, but this does not mean that an attempt has been made to prejudge the question.

have been recognized among the 68 cases had a special search been instituted. The patient with such an associated sinusitis is liable to the complications of this condition, as well as those of his bronchiectasis. Adams,[120] for instance suggested that cerebral abscess, the classic fatal complication of bronchiectasis, may often be in reality a complication of sinusitis when this is present. Indeed, he expressed the opinion that both the bronchiectasis and the abscess may be directly due to sinal infection.

The rarity of cerebral abscess in pyemic states, even when abscesses are present in the lung, was commented on by Ballon, Singer and Graham [18] and by Goodman,[16] and the frequency of cerebral abscess as a cause of death in cases of bronchiectasis seems to demand some

119. Jex-Blake.[118] Moll.[65]

120. Adams, J.: J. Laryng. & Otol. **40**:172, 1925.

such explanation as was offered by Adams. Osler and McCrae [121] cited the 13,700 autopsies at the London Hospital and the Brompton Hospital which were reported by Schörstein. Among them were 19 instances of cerebral abscess associated with pulmonary disease, usually bronchiectasis.

In table 1, in which are listed cases of death from bronchiectasis at the Royal Victoria Infirmary in the ten years from 1929 to 1938, it will be noted that intracranial abscess was the cause in 5 out of 27 cases. This incidence of intracranial abscess compares with Tuffier's [122] report of 6 instances of intracranial abscess in 45 cases, Schörstein's estimate

TABLE 2.—*Causes of Death in 55 Cases of Fatal Bronchiectasis (Moll* [65])

Bronchopneumonia	16
Empyema	10
Pyopneumothorax	3
Cardiac failure	4
Cerebral abscess	3
Gangrene of lung	2
Pulmonary abscess	1
Hemoptysis	1
Nephritis	1
Other causes	14

TABLE 3.—*Causes of Death in 110 Cases of Fatal Bronchiectasis (Jex-Blake* [118])

Bronchopneumonia	34
"Exhaustion"	34
"Exhaustion" and asphyxia	8
Cerebral abscess	15
Cerebral new growth	2
Hemoptysis	5
Heart failure	3
Postoperative collapse	3
Intercurrent disease	3
Septic diarrhea	1
Lobar pneumonia	1
Influenzal pneumonia	1

of cerebral abscess as the cause of death in 20 per cent of cases and Moll's [65] report of 3 cases of abscess of the brain in 55 cases of fatal bronchiectasis.

Finally, the death of patients suffering from bronchiectasis may be due to intercurrent disease which has no apparent connection with the bronchopulmonary condition. Only 2 examples of such death were noted in the pathologic records. One was that of a girl of 9, who died of pneumococcic peritonitis. The other occurred in a patient who died of portal pyemia, which could not be related to the bronchial disease. One

121. Osler, W., and McCrae, T.: The Principles and Practice of Medicine, ed. 9, New York, D. Appleton and Company, 1920, p. 617.

122. Tuffier: Bull. et mém. Soc. de chir. de Paris **36**:529, 1910.

patient died of acute lobar pneumonia, but his case was not included, as it was not considered possible to exclude the connection of this with preexisting bronchiectasis.

C. Infection of the Blood Stream and the Late Results of Chronic Sepsis: Only 1 apparent example of infection of the blood stream was noted in the pathologic series of 27 cases recorded at the Royal Victoria Infirmary. This was the case of a woman who died of general pyemia for which no cause apart from the bronchiectasis was to be found. This complication must be rare.

The only late results of chronic sepsis which appear to occur are amyloid disease and myocardial damage, and neither can be shown to be at all frequent as a direct cause of death. The significance of Jex-Blake's [118] 34 cases of "exhaustion" is difficult to assess. No example of either amyloid disease or myocardial damage was noted as a cause of death in the present investigation, although it is difficult to exclude the 2 instances of death from cardiac disease, cited in section A. It may be that they should have been included here, although the balance of evidence was held to be in favor of regarding them as the result of true intrathoracic complications.

SUMMARY AND CONCLUSIONS

1. Sixty-eight cases of bronchiectasis which I observed over a period of several years are reported.

2. An account of the anatomy and physiology of the normal bronchi, based on a study of the recent literature and on a dissection of a normal bronchial tree, is presented.

3. An analysis of the records of the 68 cases, including a pathologic examination of lobes excised at operation in 28 cases, is made, and the relevant literature is reviewed.

4. The pathogenesis, the etiology and the clinical and roentgenologic features of the disease are described on the basis of this analysis.

5. A classification is suggested, which recognizes congenital cystic disease of the lung and atelectatic and bronchogenic types of acquired bronchiectasis.

6. Finally, the problem of prognosis of and the causes of death from bronchiectasis are discussed. This discussion is based on the results in the 68 cases, on the autopsy records of the Royal Victoria Infirmary from 1929 to 1938, inclusive, and on a study of the literature.

7. The conclusion is reached that bronchial dilatation may be temporary or permanent. Temporary bronchiectasis is always due to collapse of the lung tissue, but permanent bronchiectasis is the result

of the interaction of many factors, of which the most important is infection of the bronchial wall.

8. The numerous pathogenic factors in the evolution of bronchiectasis are grouped under two heads: (*a*) defects in the bronchial wall and (*b*) excessive strain and stress to which the bronchial wall may be subjected.

9. The question of "congenital bronchiectasis" is left open, as no conclusive evidence of its existence apart from congenital cystic disease of the lung has been found. The difficulties in the solution of the matter are discussed.

10. The value of an accurate history and of careful physical examination in the diagnosis of bronchiectasis is emphasized. In but few cases have physical signs been absent.

11. The need for a detailed and extensive study of the prognosis in selected groups of cases is emphasized. An analysis of the present series is made in order to illustrate the suggested type of investigation of prognosis.

12. The causes of death in bronchiectasis are classified into three groups: (*a*) local exacerbation or spread of infection within the lungs or thoracic cavity; (*b*) direct complications of associated conditions and intercurrent disease, and (*c*) dissemination of infection by the blood stream and the late results of chronic sepsis.

Dr. G. Hall and Dr. T. C. Hunter gave me permission to cite cases at one time under their care in the Royal Victoria Infirmary. Prof. A. F. Bernard Shaw gave me access to and permission to quote from the pathologic records of the Royal Victoria Infirmary. Dr. S. Whately Davidson, Hon. Radiologist to the Royal Victoria Infirmary and Radiologist to the Newcastle General Hospital gave me access to and permission to cite from and reproduce roentgenograms taken at these hospitals, under his supervision. Mr. George Mason, Surgeon in Charge, Department of Thoracic Surgery, Newcastle General Hospital, and Hon. Assistant Surgeon, Royal Victoria Infirmary, gave me access to cases, records and pathologic material under his charge, and permitted me to quote and reproduce certain operative records and pathologic specimens. Dr. G. A. Smart prepared the photomicrographs.

BLOOD PRESSURE STUDIES ON WEST INDIANS AND PANAMANIANS LIVING ON THE ISTHMUS OF PANAMA

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The purposes of this paper are (1) to compare the incidence of hypertension in West Indians and Panamanians living on the Isthmus of Panama, and (2) to provide data which may be of value in considering the relation between arterial tension and such factors as race, heredity and climate.

LITERATURE

Reports on the blood pressure of various peoples and on the importance of race and climate as factors influencing blood pressure have not been numerous, and the results are inconclusive.

Philippines.—Musgrave and Sison [1] expressed the belief that blood pressure in persons living in the tropics is low. The average systolic blood pressure for 30 native males was 108 mm. of mercury and for 19 females 113 mm. Figures given for foreigners included 124 mm. after one year of residence, 115 mm. after one to five years of residence and 113 mm. after ten years of residence. Chamberlain [2] stated that the average systolic blood pressure of American soldiers stationed in the Philippines was 115 mm. for ages 18 to 30 and 118 mm. for ages 30 to 40. Filipinos had almost identical blood pressures. He claimed that, except for a slight fall during the first three months, there was no tendency for the blood pressure to drop with increasing time of residence in the Philippines. Concepción and Bulatao [3] reported similar findings but drew different conclusions. The average blood pressure of 717 males with an average age of 28.5 years was 115 mm. systolic and 79 mm. diastolic and for females 116 mm. systolic and 83 mm. diastolic. They concluded that the blood pressures of Filipinos were lower than those of Americans living in the United States but the same as those of Americans

From the Board of Health Laboratory, Gorgas Hospital.

1. Musgrave, W. E., and Sison, A. G.: Blood Pressure in the Tropics, Philippine J. Sc. B **5**:325, 1910.

2. Chamberlain, W. P.: A Study of Systolic Blood Pressure and Pulse Rate of Healthy Adult Males in the Philippines, Philippine J. Sc. B **6**:467, 1911.

3. Concepción, I., and Bulatao, E.: Blood Pressure of Filipinos, Philippine J. Sc. B **11**:135, 1916.

living in the Philippines. Siler [4] observed: "Blood pressures in the general run of individuals living in tropical countries are maintained at lower levels than in temperate or colder climates."

China.—Cadbury [5] wrote: "Hypertension as a pathological condition is rare in China." The average systolic blood pressure of Cantonese students was 20 to 30 mm. less and the average diastolic blood pressure 10 to 20 mm. less than those of Europeans and North Americans. Kilborn [6] reported that blood pressures of persons living in China tended to be low. Tung [7] revealed that the average blood pressure of Americans dropped from 118 mm. systolic and 76 mm. diastolic to 109 mm. systolic and 65 mm. diastolic after three years' residence in Peiping. Foster [8] stated: "The blood pressure of the Chinese is lower than the general average for western countries. Foreigners living in China tend to develop lower blood pressures." Of 4,000 Chinese patients in the Hunan-Yale Hospital only 20 were found to have a blood pressure over 160 mm. Twenty-two of 33 Americans showed a fall of blood pressure after residence in China.

Japan.—Tanemura [9] reported that the average blood pressure of males aged 19 was 122 mm. systolic and 83 mm. diastolic.

Egypt.—Ismail [10] claimed that 10 per cent of all his private patients had essential hypertension.

India.—McCay,[11] using the palpatory method on 500 male Bengalis aged 20 to 25, found that the systolic blood pressure was 90 to 105 mm., while the range for Europeans in Calcutta was 115 to 130 mm.

Australia.—Nye [12] denied the presence of hypertension in the Australian aborigines.

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4. Siler, J. F.: Annual Physical Examinations of Officers in the Philippine Islands, Mil. Surgeon **56**:738, 1925.

5. Cadbury, W. W.: The Blood Pressure of Normal Cantonese Students, Arch. Int. Med. **30**:362 (Sept.) 1922.

6. Kilborn, L. G.: Blood Pressure of Szuchaenese Students, China M. J. **40**: 1, 1926.

7. Tung, C. L.: Relative Hypotension of Foreigners in China, Arch. Int. Med. **40**:153 (Aug.) 1927.

8. Foster, J. H.: Blood Pressure of Foreigners in China, Arch. Int. Med. **40**: 38 (July) 1927; Practice of Medicine in China and New England with Observations on Hypertension, New England J. Med. **203**:1073, 1930.

9. Tanemura, I.: Kyoto J. M. Sc. **15**:84, 1918; cited by Cadbury.[5]

10. Ismail, Abd-El-Aziz: Etiology of Hyperpiesis in Egyptians, Lancet **2**: 275, 1928.

11. McCay, D.: Lancet **1**:1483, 1907, cited by Cadbury; [5] Scientific Memoirs of Government of India, 1908, no. 34, p. 23; cited by Cadbury.[5]

12. Nye, L. J. J.: Blood Pressure in the Australian Aboriginal with Consideration of Possible Aetological Factors in Hyperpiesia and Its Relation to Civilization, M. J. Australia **2**:1000, 1937.

Africa.—Donnison [13] reported that the blood pressures of Negroes living under primitive native conditions were similar to those of white persons up to the age of 40. After 40 the blood pressure of white persons increased, while those of Negroes declined.

United States.—Alvarez and Stanley [14] noted that older Mexican prisoners rarely showed an increase in blood pressure. The tension of Negro prisoners was higher than normal. Allen [15] found that 55.6 per cent of 1,000 Negro factory workers in Cleveland and 33.5 per cent of 2,000 white workers had cardiovascular abnormalities. Hypertension constituted 45 per cent of the cardiovascular abnormalities. Adams [16] recorded slightly higher average blood pressures for Negro workmen than for white workmen in New Orleans. Lemann [17] was unable to find remissions of high blood pressures in 45 patients during a long, continued, subtropical summer in New Orleans. Flaxman [18] found that hypertension was more common among Negroes than among white persons in the Middle West and that they died of heart disease earlier. Schultze and Schwab [19] noted that there was a greater incidence of hypertension in Southern Negroes than in white persons.

Arctic Region.—Firestone [20] found that Eskimos had the same incidence of hypertension as was reported for inhabitants of the United States.

West Indies.—Roddis and Cooper [21] observed that the average systolic blood pressure of 67 officers of the United States Navy on temporary duty in the West Indies was 11.4 mm. less than the average for a similar group of men living in the United States. They noted a gradual rise in the blood pressures of 16 officers on return to colder climates.

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13. Donnison, C. P.: Blood Pressure in African Natives, Lancet **1**:6, 1929.

14. Alvarez, W. C., and Stanley, L. L.: Blood Pressures in Six Thousand Prisoners and Four Hundred Prison Guards, Arch. Int. Med. **46**:17 (July) 1930.

15. Allen, F. P.: Cardio-Vascular Impairment Among One Thousand Negro Factory Workers, J. Indust. Hyg. **13**:164, 1931.

16. Adams, J. M.: Some Racial Differences in Blood Pressures and Morbidity in a Group of White and Colored Workmen, Am. J. M. Sc. **184**:342, 1932.

17. Lemann, I. I.: Effect of a Long Continued Subtropical Summer on High Blood Pressure, Am. J. Trop. Med. **12**:331, 1932.

18. Flaxman, N.: Heart Disease in the Middle West, Am. J. M. Sc. **188**:639, 1934.

19. Schultze, V. E., and Schwab, E. H.: Arteriolar Hypertension in American Negroes, Am. Heart J. **11**:66, 1936.

20. Firestone, cited by Blackford, J. M.; Bowers, J. M., and Baker, J. W.: Follow-Up Study of Hypertension, J. A. M. A. **94**:328 (Feb. 1) 1930.

21. Roddis, L. H., and Cooper, G. W.: The Effect of Climate on Blood Pressure, J. A. M. A. **87**:2053 (Dec. 18) 1926.

Panama.—Thonnard-Neumann [22] recorded a systolic blood pressure of over 140 mm. in 33.5 per cent of 500 West Indians living in Panama. The average age was 40.

STUDY I

Col. Robert M. Hardaway, chief of the medical service of Gorgas Hospital, was impressed by the difference in the incidence of hypertension between West Indians and Panamanians.[23] An opportunity to analyze phases of this difference presented itself when, after years of simple operation and maintenance, the government embarked on an extensive building program for the Panama Canal. Within a few months, several thousand candidates for employment were given a complete physical examination.

Method.—1. The statistics were gathered on 1,328 consecutive male candidates for employment on the Silver Roll of the Panama Canal between October 1939 and April 1940. (The Silver Roll employs unskilled or slightly skilled laborers, generally Panamanians and West Indians, whereas the Gold Roll employs, for the most part, skilled Americans.)

2. The readings were taken under identical conditions for the two race groups by one observer, who examined 25 to 35 men daily.

3. One new mercury sphygmomanometer, which had been checked for accuracy by the United States Bureau of Standards, was used.

4. On completion of a routine physical examination, the candidates were permitted to rest for fifteen to thirty minutes. Readings were then taken on each seated candidate at three minute intervals until two consecutive systolic readings were within 6 mm. of mercury of each other. In a few cases this technic was only approximated.

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22. Thonnard-Neumann, E.: Blood Pressure Studies in the West Indian Negroes, 18th Annual Report, Medical Department, United Fruit Company, Boston, 1929, p. 251.

23. Three fairly distinct race groups live on the Isthmus of Panama: Panamanians, West Indians and Americans.

By appearance, background, customs and language, these groups are easily separated. Of course, none of these groups meets the anthropologist's definition of "race." In this paper the term "race" is used colloquially, with appreciation of its scientific limitations.

The original Panamanian was an Indian. To his stock, for 300 years, has been added the blood of Europeans, Negroes, Chinese, etc. Today the Panamanian, especially of the cities, is a "Latin American."

When the Panama Canal was built, thousands of Negroes from Jamaica, the Barbados and other West Indian islands were imported as laborers. The ancestors of these Negroes had mixed to an indeterminate degree with many peoples since their transfer from Africa. Nevertheless, in Panama these Negroes and their families constitute a fairly definite group.

TABLE 1.—*Results of Study I*

Panamanians (P.) or West Indians (W. I.)	Age 16 to 25		Age 26 to 35		Age 36 to 45		Age 46 to 65		Total	
	P.	W. I.	P.	W. I.	P.	W. I.	P.	W. I.	P.	W. I.
Number of candidates	393	312	276	113	64	54	54	62	787	541
Percentage of race total	49.9	57.7	35.1	20.9	8.1	10.0	6.9	11.5	100	100
Average age, year	21.2	20.6	29.1	29.5	39.1	41.2	49.6	51.6	27.1	28.1
Average systolic blood pressure	104.9	114.5	106.6	117.8	102.9	127.2	115.0	135.8	105.6	119.0
Average diastolic blood pressure	72.2	78.1	73.9	82.0	76.3	88.8	76.9	91.6	74.9	81.7
Number with systolic blood pressure of 150 and over	1	13	2	8	2	11	5	21	10	53
Percentage with systolic blood pressure of 150 and over	0.3	4.2	0.7	7.1	3.1	20.4	9.3	33.9	1.3	9.8
Number with systolic blood pressure of 170 and over	0	6	1	4	1	4	1	13	3	27
Percentage with systolic blood pressure of 170 and over	0	1.9	0.4	3.5	1.6	7.4	1.9	21.0	0.4	5.0
Number with diastolic blood pressure of 100 and over	2	8	6	12	2	14	3	19	13	53
Percentage with diastolic blood pressure of 100 and over	0.5	2.6	2.2	10.6	3.1	25.9	5.6	30.6	1.7	9.8
Number with diastolic blood pressure of 120 and over	0	2	1	2	1	4	0	6	2	14
Percentage with diastolic blood pressure of 120 and over	0	0.6	0.4	1.8	1.6	7.4	0	9.7	0.3	2.6
Number with systolic blood pressure of 100 and under	172	77	99	23	26	7	11	7	308	114
Percentage with systolic blood pressure of 100 and under	43.8	24.7	35.9	20.4	40.6	13.0	20.4	11.3	39.1	21.1
Number with systolic plood pressure of 80 and under	19	9	19	1	7	1	1	3	46	14
Percentage with systolic blood pressure of 80 and under	4.8	2.9	6.9	0.9	10.9	1.9	1.9	4.8	5.8	2.6
Number with diastolic blood pressure of 60 and under	43	17	38	0	6	1	5	2	92	20
Percentage with diastolic blood pressure of 60 and under	10.9	5.4	13.8	0	9.4	1.9	9.3	3.2	11.7	3.7

5. Systolic blood pressure was read at the sudden appearance of a clear sound as the mercury column fell (beginning of first phase). Diastolic blood pressure was read at the initial replacement of the clear sounds by a muffled sound (fourth phase).

Definitions.—1. A "Panamanian" is one born in Panama whose parents were both born in Panama.

2. A "West Indian" is a Negro who was either born in the West Indies of West Indian parentage or whose parents both were born in the West Indies.

3. "Average blood pressure" of a person consists of the average of all the readings taken on that person. (A total of 3,388 readings were taken on 1,328 candidates, for an average of 2.6 readings for each person.)

Results.—These are summarized in table 1.

Comment.—1. The incidence of hypertension was much greater in West Indians than in Panamanians in each age group. Ratios were 16:1 for ages 16 to 25, 10:1 for ages 26 to 35, 7:1 for ages 36 to 45, 4:1 for ages 46 to 65 and 7:1 for the entire group.

2. The incidence of hypotension was much greater in Panamanians than in West Indians.

3. The age distribution of the candidates in each race group was almost identical.

4. The average blood pressures should not be given great significance because these averages include those of subjects with hypertension.

STUDY II

Since all the blood pressure readings in study I were taken by one observer, confirmatory evidence for the appreciable difference in the incidence of hypertension between West Indians and Panamanians was sought.

Method.—1. The records of 7 physicians doing the physical examinations were analyzed.

2. These physicians examined 40 to 100 men daily under conditions that were not especially adapted for blood pressure studies.

3. Several sphygmomanometers were used.

4. No attempts were made to standardize the time and technic of taking the blood pressures.

5. Only one reading was generally taken. When the initial reading was high and further observations were made, that reading which the individual examiner considered as final was utilized.

6. The same definitions of "Panamanian" and "West Indian" used in study I prevailed.

Results.—These are summarized in table 2.

Comment.—The records of the 7 physicians corroborate the findings in study I. The higher incidence of hypertension in both groups can be explained by the fact that in study II the blood pressure readings were taken under uncontrolled conditions, in which excitement may have been an important factor. Sufficient readings were not taken to eliminate that possibility. The ages were not studied because the results of study I indicated that the age distributions of the candidates of the two race groups were almost identical.

TABLE 2.—*Results of Study II*

Race Group	Total Number of Candidates	Number with Systolic Blood Pressure of 150 and Over	Percentage with Systolic Blood Pressure of 150 and Over
Panamanians	2,457	158	6.4
West Indians	745	175	23.5

TABLE 3.—*Results of Study III*

Race Group	Total Number of Women	Number with Systolic Blood Pressure of 150 and Over	Percentage with Systolic Blood Pressure of 150 and Over
Panamanians	410	12	2.9
West Indians	1,301	139	10.7

STUDY III

An entirely different group of persons was sought for further confirmation of the results of study I. Dr. Howard K. Tuttle permitted the use of the records of his large antepartum clinic.

Method.—1. The antepartum records from 1936 to 1940 were analyzed.

2. Only those cases were considered in which two or more readings of blood pressure were available.

3. The blood pressure reading at the initial visit was disregarded because the patient usually was excited on that visit.

4. Those subjects for whom a single reading on any of the visits, except the first, was 150 mm. or over were considered in the hypertensive group.

5. It was impossible to question the patients as to their birthplace, parents, etc., as was done in the first two studies. The distinction between Panamanian and West Indian was made on the basis of name alone; that is, when the name was "Spanish" the patient was considered Panamanian and when the name was "British" the patient was considered West Indian. Doubtful cases were disregarded. The person who "decided" the nationality of the patients has lived on the Isthmus for over twenty years and has had much experience with hospital patients. Records of the blood pressure were concealed until the decision was made, to avoid unintentional prejudice.

Results.—These are summarized in table 3.

Comment.—Although the possibility of error in distinguishing between Panamanian and West Indian has been introduced, it is believed that the error cannot be of significance.

TABLE 4.—*Summary of Answers to Questionnaires*

Questionnaires sent	110
Replies received	68
Opinion that incidence of hypertension is higher in West Indians	45
Opinion that incidence of hypertension is higher in Panamanians	2
Members unqualified or unwilling to give impression	21

STUDY IV

Method.—1. A questionnaire was sent to all members of the Medical Association of the Isthmian Canal Zone requesting their impressions as to the relative incidence of hypertension in West Indians and Panamanians.

Results.—The answers to the questionnaire are summarized in table 4.

COMMENT

The results of the four studies are in harmony and indicate that (*a*) the incidence of high blood pressure is much greater in West Indians than in Panamanians, and that (*b*) the incidence of low blood pressure is much greater in Panamanians than in West Indians.

The standards used in determining the presence of hypertension were high. A systolic blood pressure of 150 mm. is certainly abnormal under conditions of rest. If 140 mm. had been used the incidence of hypertension would have been higher in both groups, but the ratios would not have been altered.

Reaction of the West Indians and their descendants to a strange environment might have been responsible for the hypertension. How-

ever, reports from Phillips [24] indicate that the Negroes in Jamaica have a high incidence of hypertension.

The high incidence of hypotension in Panamanians, as is demonstrated in table 1, seems to substantiate in part the views of Robinson and Brucer [25] that levels of normal blood pressure must be revised downward. The evidence that hypotension is a disease or an important sign of one, except in such rare conditions as Addison's disease, has never been convincing. The possibility that tuberculosis or anemia may be responsible for hypotension in Panamanians exists, but it is my impression that hypotension is normal tension in Panama and elsewhere.

A high incidence of hypertension may be present among persons living in a tropical country.

The influence of heredity as a factor in hypertension is receiving increased consideration. Fishberg [26] stated: "In at least a large majority of instances essential hypertension arises on the basis of an inherited constitutional predisposition." The work of Hines [27] also indicated the importance of heredity in the problem of hypertension.

It should be understood distinctly that no attempt is being made to attribute the difference in arterial tension between West Indians and Panamanians to the difference in race. Neither group is a true race. Studies on the psychology, occupations, diet, habitus, anatomy and diseases of both peoples must be made before the etiologic factors for the differences will be apparent.

SUMMARY

1. Nine and eight-tenths per cent of 541 male West Indians living in Panama had an average systolic blood pressure of 150 mm. or over when the studies were made under controlled conditions. One and three-tenths per cent of 787 Panamanians tested under the same conditions had a systolic blood pressure of 150 mm. or over.

2. Twice as many Panamanians as West Indians had low blood pressures.

3. The average blood pressure of male candidates for employment, with ages ranging from 16 to 65, was 119 mm. systolic and 82 mm. diastolic, for West Indians, and 106 mm. systolic and 75 mm. diastolic, for Panamanians.

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24. Phillips, C. B.: Reports to the Chief Health Officer, Canal Zone, 1940, unpublished data.

25. Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure, Arch Int. Med. **64**:409 (Sept.) 1939.

26. Fishberg, A. M.: Hypertension and Nephritis, ed. 2, Philadelphia, Lea & Febiger, 1939, p. 613.

27. Hines, E. A., Jr.: The Heredity Factor and Subsequent Development of Hypertension, Proc. Staff Meet., Mayo Clin. **15**:145, 1940.

4. Twenty-three and five-tenths per cent of 745 other West Indians had a systolic blood pressure of 150 mm. or over when the readings were taken under uncontrolled conditions. Six and three-tenths per cent of 2,457 other Panamanians had a systolic blood pressure of 150 mm. or over under the same conditions.

5. Ten and seven-tenths per cent of 1,301 pregnant West Indian women had a single systolic blood pressure reading of 150 mm. or over while attending an antepartum clinic. Two and nine-tenths per cent of 410 Panamanian women had such a reading under like conditions.

6. Forty-five physicians of the Medical Association of the Isthmian Canal Zone thought West Indians have a higher incidence of hypertension than Panamanians. Two physicians thought that the incidence is higher in Panamanians.

Brig. Gen. Morrison C. Stayer, Chief Health Officer, Canal Zone, provided facilities for this work.

TRANSMISSION OF ANTIANEMIC PRINCIPLE ACROSS THE PLACENTA AND ITS INFLUENCE ON EMBRYONIC ERYTHROPOIESIS

I. QUANTITATIVE EFFECT OF DIETS CONTAINING VENTRICULIN

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Studies of anemia in pregnancy [1] have directed attention to the hypothesis that the mother may not always have an adequate supply of blood-building material for both fetal and maternal demands and that the fetus may deplete the maternal stores regardless of the result to the mother.[2] More specifically, Wintrobe and Shumacker [3] suggested that a macrocytic anemia might develop during pregnancy if the fetus derived its supply of antianemic principle from the mother to the extent that a deficiency was caused to exist in the storage of maternal liver factor. If this assumption is correct, one should be able to influence embryonic and fetal erythropoiesis by supplying the mother with a superabundance of antianemic principle. Although Wintrobe and associates [4] were unable to influence the red cell count and the mean corpuscular volume of 21 and 23 day rabbit fetuses, they expressed the belief that this did not contradict their hypothesis because they assumed the addition of more antianemic principle to a fetus already supplied with a maximal quantity from the mother could not be expected to produce any significant effect. On the basis of the morphologic similarity between fetal blood and that

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1. Strauss, M. B., and Castle, W. B.: Studies of Anemia in Pregnancy: II. The Relationship of Dietary Deficiency and Gastric Secretion to Blood Formation During Pregnancy, Am. J. M. Sc. **184**:663 (Nov.) 1932.

2. Strauss, M. B., and McDonald, W. J.: Polyneuritis of Pregnancy a Dietary Deficiency Disorder, J. A. M. A. **100**:1320 (April 29) 1933.

3. Wintrobe, M. M., and Shumacker, H. B.: Comparison of Hematopoiesis in the Fetus and During Recovery from Pernicious Anemia, Together with a Consideration of the Relationship of Fetal Hematopoiesis to Macrocytic Anemia of Pregnancy and Anemia in Infants, J. Clin. Investigation **14**:837 (Nov.) 1935.

4. Wintrobe, M. M.; Kinsey, R. E.; Blount, R. C., and Trager, W.: Studies of Blood Formation in the Fetus and Newborn: III. The Relationship of Anti-Anemic Principle, Assay of Fetal Liver and Placental Extracts in Cases of Pernicious Anemia and in Mosquito Larvae, Am. J. M. Sc. **193**:449 (April) 1937.

taken during relapse from patients with pernicious anemia, Wintrobe and Shumacker [8] concluded that the blood of the newborn infant or of the fetus in the terminal stages of development is similar to that in patients with pernicious anemia during various phases of therapeutically induced remission. Chiefly because of these quantitative similarities, Stasney and Higgins [5] selected the newborn rat as a suitable animal in which to study the effect of concentrated gastric juice administered intraperitoneally to the mother during the latter part of pregnancy. Both normal human and hog gastric juices produced significant changes in the red corpuscles of the newborn rat.[6] Later Higgins and his students [7] also reported that human gastric juice (administered orally), reticulogen (a liver extract with vitamin B_1, administered parenterally), extralin (a liver-stomach concentrate) and ventriculin (a desiccated preparation of hog stomach) administered during gestation accelerated fetal erythropoiesis. More recently Stasney and Burns [8] have reported significant changes in the blood of opossum pouch young following the administration of concentrated normal gastric juice and concentrated solution of

5. Stasney, J., and Higgins, G. M.: The Effect of Normal Human Gastric Juice Administered to the Mother on the Size and Volume of the Erythrocytes of the Fetus, Proc. Staff Meet., Mayo Clin. **12**:490 (Aug. 4) 1937.

6. (*a*) Stasney and Higgins.[5] (*b*) Stasney, J.; Higgins, G. M., and Mann, F. C.: The Size, Volume and Number of Erythrocytes of the Newborn Rat: Effect of Administration, to the Mother, of Gastric Juice of a Normal Hog, Proc. Staff Meet., Mayo Clin. **12**:699 (Nov. 3) 1937; (*c*) The Effect on the Developing Red Blood Cells in the Fetus of Administering Human and Hog Gastric Juice to the Adult Rat During Pregnancy, Am. J. M. Sc. **197**:690 (May) 1939.

7. (*a*) Briese, E., and Higgins, G. M.: The Effect of Feeding Ventriculin to Pregnant Rats, with Special Reference to the Size of the Red Blood Cells of the Young, Anat. Rec. **73**:105 (Jan.) 1939. (*b*) Higgins, G. M.: Personal communication to the author, regarding effect of extralin and reticulogen. (*c*) Schlicke, C. P.: The Effect of Normal and Abnormal Human Gastric Juice, Administered to the Mother, on the Blood of Newborn Rats: Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**:145 (March 8) 1939; (*d*) The Blood of Newborn Rats After Oral Administration to the Mother of Normal and Abnormal Human Gastric Juice, Am. J. M. Sc. **200**:155 (Aug.) 1940.

8. Stasney, J., and Burns, E. L.: Influence of Anti-Anemic Principles upon Size of Erythrocytes of Opossums (*Didelphis virginiana*) in Maternal Pouch, Proc. Soc. Exper. Biol. & Med. **42**:544 (Nov.) 1939; The Influence of Active and Inactive Anti-Anemic Principles upon the Size of the Erythrocytes of Opposums (*Didelphis virginiana*) in the Maternal Pouch, Am. J. Path. **17**:466 (May) 1941. Recently, Hays and Last (The Action of Liver Extract on the Size of Erythrocytes of the Opossum Embryo, J. Biol. Chem. **140**:lv [July] 1941) reported that they were unable to verify these experiments. It is difficult to evaluate the work on cell diameters by Stasney and Burns, since they measured only the largest cells in a given blood smear. Such a procedure introduces too much of the personal factor.

liver extract. Wigodsky and Ivy [9] have been unable to confirm these results in rats. This may be due to the differences in the technic of measuring the cells, and according to a recent review by Schalm [10] the method employed by Higgins and associates is the more accurate one. Bruner [11] has also reported similar negative results after injecting liver extract into pregnant rats as well as into young rats 4 to 24 days old. These negative results have been interpreted by Wigodsky and Ivy [9] to substantiate Wintrobe and Shumacker's assumption [8] that the addition of more antianemic principle to a system already adequately supplied should have no influence on the red cell picture of these animals.[12] Undoubtedly both Wintrobe and Ivy and their associates have overlooked the prehepatic, or primitive, generation of red cells in the embryo. These cells proliferate, elaborate pigment and commence to mature before the liver is morphologically differentiated. It must be remembered, however, that functional differentiation cannot be determined by the anatomic condition of an organ [13] and may even appear earlier than anticipated.[14] Regardless of whether antianemic principle is present in the various fetal livers as reported,[15] or is absent,[4] the primitive erythroblasts of the embryonic prehepatic period which are different from both definitive

9. Wigodsky, H. S., and Ivy, A. C.: Effect of Liver Extract, Injected Parenterally into Pregnant Mother, on Erythrocytes of Newborn Rats, Proc. Soc. Exper. Biol. & Med. **38**:787 (June) 1938. Noble, T. A.; Wigodsky, H. S., and Ivy, A. C.: Effect of Gastric Juice on Erythrocytes of Newborn Rats, ibid. **45**:373 (Oct.) 1940.

10. Schalm, L.: The Determination of the Mean Red Blood Cell Diameter and Its Clinical Value, Folia haemat. **63**:34, 1939.

11. Bruner, H. D.: Effect of Parenteral Liver Extract on the Blood Picture of New Born Rats, Proc. Soc. Exper. Biol. & Med. **41**:260 (May) 1939.

12. Fitz-Hugh, Creskoff and Taylor attempted to stimulate reticulocyte maturation by injecting liver extract parenterally into 9 individual rat fetuses in utero, but no significant change from the normal reticulocyte curve was obtained (J. Clin. Investigation **15**:468 [July] 1936).

13. Meulengracht, E.: Histologic Investigation into the Pyloric Gland Organ in Pernicious Anemia, Am. J. M. Sc. **197**:201 (Feb.) 1939.

14. Dalton, A. J.: The Functional Differentiation of the Hepatic Cells of the Chick Embryo, Anat. Rec. **68**:393 (July) 1937. Heuser, C. H.: The Early Establishment of the Intestinal Nutrition in the Opossum: The Digestive System Just Before and Soon After Birth, Am. J. Anat. **28**:341 (Nov.) 1921.

15. Berglund, H.; Watkins, C. H., and Johnson, R.: Rapid Stimulation of Hemoglobin Synthesis in Secondary Anemias After Feeding Fetal Calf's Liver, Proc. Soc. Exper. Biol. & Med. **25**:814 (June) 1928. Goldhamer, S. M.; Isaacs, R., and Sturgis, C. C.: The Rôle of the Liver in Hematopoiesis, Am. J. M. Sc. **188**:193 (Aug.) 1934. Wigodsky, H. S.; Richter, O., and Ivy, A. C.: The Presence of the Antipernicious Anemia Factor in an Extract of Fetal Bovine Livers, ibid. **197**:750 (June) 1939. Sharp, E. A.: Personal communication to the author.

erythroblasts and megaloblasts [16] occurring in pernicious anemia do differentiate and mature at a slow rate. The differentiation of these primitive erythroblasts in tissue culture [17] might be interpreted to indicate that it occurs in the absence of an erythrocyte-maturing principle or that the latter was present only in minute quantities.

The primitive red cells of the prehepatic period are formed intravascularly in the yolk sac and have been called megaloblasts by some authors,[18] although the term primitive erythroblast first suggested by Maximow is a more appropriate one. According to Bloom [19] and Kirschbaum,[20] definitive erythroblasts, or cells of the normoblastic series, are not formed in the rat yolk sac. Thus far my studies of the 11 day rat embryonic yolk sac have substantiated these claims. The primitive erythroblasts of the rat yolk sac have been described by Kirschbaum [20] as similar to the megaloblasts occurring in pernicious anemia but not identical with them. He expressed the belief that the differences in nuclear structure of these two hemoglobiniferous cell types cannot be explained on the basis of species variability alone.[21] The nuclear pattern of the primitive erythroblast becomes coarser earlier and is more "normoblastic" than the chromatin pattern of genuine megaloblasts (plate III, Jones [16b]). The embryonic primitive erythroblasts are further dis-

16. (*a*) Jones, O. P.: The Origin and Structure of Erythroblasts with Special Reference to the Megaloblast, Thesis, University of Minnesota, Graduate School, 1935; (*b*) Cytology of Pathologic Marrow Cells, with Special Reference to Bone Marrow Biopsies, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 2043; (*c*) Nature of the Reticulocytosis in Pernicious Anemia Following Liver Therapy, Proc. Soc. Exper. Biol. & Med. **38**:222 (March) 1938; (*d*) Transmission of Antianemic Principle Across the Placenta and Its Effect on the Primitive Erythroblasts of the Eleven-Day Rat Embryo, Anat. Rec. **73** (supp. 3):29 (March 25) 1939; (*e*) Further Studies of the Transmission of Antianemic Principle Across the Placenta and Its Effect on the Primitive Erythroblasts of the Eleven-Day Rat Embryo, ibid. **76** (supp. 2):34 (Feb.) 1940. (*f*) Kirschbaum, A.: Blood Cell Formation in Mammalian Embryos from the First Appearance of Vascular Cellular Elements Through the Period of Hepatic Hemopoiesis, Thesis, University of Minnesota, Graduate School, 1936; (*g*) Cytological Studies of Mammalian Embryonic Blood Cells, Proc. Soc. Exper. Biol. & Med. **35**:542 (Jan.) 1937.

17. Bloom, W.: Cellular Differentiation and Tissue Culture, Physiol. Rev. **17**: 589 (Oct.) 1937. Maximow, A.: Tissue Cultures of Young Mammalian Embryos, Contrib. Embryol. (no. 80) **16**:47, 1925.

18. Sabin, F. R.: Studies on Blood: The Vitally Stainable Granules as a Specific Criterion for Erythroblasts and the Differentiation of the Three Strains of the White Blood-Cells as Seen in the Living Chick's Yolk-Sac, Bull. Johns Hopkins Hosp. **32**:314 (Oct.) 1921.

19. Bloom, W.: Embryogenesis of Mammalian Blood, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 2, p. 863.

20. Kirschbaum (footnotes 16 *f* and *g*).

21. Jones,[16b] p. 2060. Kirschbaum (footnotes 16 *f* and *g*).

tinguished from the pathologic megaloblasts by their inability to enucleate rapidly and the relatively infrequent occurrence of karyorrhexis.[20] No early developmental stage of the prehepatic generation of red cells is to be found in the fetal liver, fetal spleen or adult bone marrow.[22] Thus it can be appreciated that embryonic blood during the prehepatic period furnishes a ready source of cells which are normally similar to the megaloblasts occurring in pernicious anemia. The importance of this is further emphasized by the fact that so far it has been either difficult [23] or impossible to produce by experimental methods [24] cells which are morphologically indistinguishable from the genuine megaloblasts occurring in pernicious anemia.[16] Schwarz [25] expressed the opinion that the similarity of the embryonic cells to megaloblasts is due to the functionally undifferentiated liver present during the embryonic period; consequently the erythropoiesis is like that found in the marrow from patients with anemias due to liver principle deficiency. Because of these morphologic similarities the embryonic blood cells might react to various antianemic substances in a manner similar to that of the marrow cells in patients with pernicious anemia after specific antianemic therapy. Blood from 11 day rat embryos was considered appropriate for studies of this nature for several reasons.[16] All of the hemoglobiniferous cells are nucleated. The chromatin is definitely stippled in a fairly coarse and irregular fashion, and the nucleoli are prominent. Marked nuclear condensation, pyknosis, karyorrhexis and karyolysis are either absent or extremely rare. Most of the cells have a highly basophilic cytoplasm. A fairly homogeneous population of cells like this should be suitable for determining the relative effects of erythrocyte-maturing factors on the nucleus, as well as on the cytoplasm. It might also serve to throw some light on such a controversial question as the fate of megaloblasts in cases of pernicious anemia after therapy. This has been supported, on the one hand, by Bock and Malamos,[26] Fieschi,[27] Jones,[27a] Naegeli,[24] Rohr,[28] Segerdahl,[29] Storti [30]

22. Bloom.[19] Kirschbaum (footnotes 16*f* and *g*).

23. Wills, L., and Stewart, A.: Experimental Anaemia in Monkeys with Special Reference to Macrocytic Nutritional Anaemia, Brit. J. Exper. Path. **16**: 444 (Oct.) 1935.

24. Naegeli, O.: Ueber die Entstehung und Behandlung der Anämien, Wien. klin. Wchnschr. **48**:225, 1935.

25. Schwarz, E.: Megaloblastische Blutbildung und Leber, Wien. klin. Wchnschr. **41**:192, 1928.

26. Bock, H. E., and Malamos, B.: Beiträge zur Megaloblastenfrage (Beobachtungen an Blut und Knochenmark im Verlaufe einer Ueberbehandelten Anaemia perniciosa), Folia haemat. **62**:408, 1939.

27. Fieschi, A.: Semeiologia del midollo osseo: Studio di morfologia clinica, in Ferrata, A.: Biblioteca "Haematologica," Pavia, Tipografa già Cooperativa, 1938, vol. 6.

27a. Jones (footnote 16*a-d*).

and others, who have maintained that the megaloblasts occurring in patients with pernicious anemia complete their maturation as megalocytes and are not transformed into cells of the definitive, or normoblastic, series. On the other hand, Doan,[31] Henning,[32] Isaacs,[33] Lambin and de Weerdt,[34] Peabody,[35] Sabin and Miller,[36] Schulten [37] and Schartum-Hansen [38] have maintained that megaloblasts are transformed into cells of the normal, or definitive, series. Furthermore, Sabin [18] even expressed the belief that embryonic primitive erythroblasts (her original megaloblasts) serve as the precursors of normoblasts.

Undoubtedly, Wintrobe, Ivy and Higgins and their associates had in part somewhat similar aims as their ultimate goal when they undertook the studies of blood from the late fetus and newborn animal. However, these authors did not exercise the proper care in carrying over ideas obtained from studying anemias in the human being and applying them to the blood of the fetus and newborn of different animals. These difficulties have arisen primarily because quantitative studies of the blood picture have been emphasized to the almost complete exclusion of the qualitative studies. The macrocytic blood picture in the late stages of development of the pig and human fetuses studied by Wintrobe and Shumacker [3] is not produced by a megalocytosis similar to that seen in

28. Rohr, K.: Die diagnostische Bedeutung die Sternalpunktion, Helvet. med. acta **1**:713, 1935; Knochenmarks-Morphologie des menschlichen Sternalpunktates, Berlin, Urban & Schwarzenberg, 1937; Das menschliche Knochenmark, Leipzig, Georg Thieme, 1940.

29. Segerdahl, E.: Ueber Sternalpunktionen, Uppsala, Appelbergs Boktryckeriaktiebolag, 1935.

30. Storti, E.: Studio in vivo del midollo osseo nell'anemia perniciosa, Haematologica **18**:1, 1937; La puntura sternale nella practica clinica, Gazz. d. osp. **59**: 807, 1938.

31. Doan, C. A.: Bone Marrow: Normal and Pathologic Physiology with Special Reference to Diseases Involving the Cells of the Blood, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3. p. 1839.

32. Henning, N.: Die Bedeutung der intravitalen Knochenmarksuntersuchung für die klinisch-hämatologische Diagnostik, Deutsche med. Wchnschr. **39**:1543, 1935; Ueber die bisherigen Ergebnisse der intravitalen Knochenmarksuntersuchung, Med. Klin. **16**:542, 1936.

33. Isaacs, R.: The Erythrocytes, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 1, p. 1.

34. Lambin, P., and de Weerdt, W.: Le problème des mégaloblastes, Rev. belge sc. med. **10**:282 (April) 1938.

35. Peabody, F. W.: The Pathology of the Bone Marrow in Pernicious Anemia, Am. J. Path. **2**:179 (May) 1927.

36. Sabin, F. R., and Miller, F. R.: Normal Bone Marrow, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 1789.

37. Schulten, H.: Die Sternalpunktion als diagnostische Methode, Leipzig, Georg Thieme, 1937; Zum Megaloblastenproblem, Folia haemat. **57**:189, 1937.

38. Schartum-Hansen, H.: Zur Morphologie des Sternalpunktates bei perniziöser Anämie und makroblastischen Anämien, Folia haemat. **58**:145, 1937.

persons with pernicious anemia, for, contrary to Dameshek and Valentine [39] and others,[40] megaloblasts are not present in the fetal liver.[16] The mere fact that normoblasts in the liver are larger than those in the adult bone marrow does not warrant the conclusion that they are megaloblasts. Cytologically the cells formed in the liver are quite different from megaloblasts and primitive erythroblasts.[16f] On the other hand, if the macrocytic blood picture in the late stages of development of the pig and human fetus is likened to any anemia,[4] it should be the macrocytic anemia seen in cases of atrophic hepatic cirrhosis in which there is a macronormoblastic marrow.[41] Recently other authors,[42] while emphasizing that liver principle–deficient anemias have a megaloblastic bone marrow, have pointed out that all megalocytic anemias are macrocytic but all macrocytic anemias are not necessarily megalocytic. Therefore, it would be unjustifiable to deduce the presence of megaloblasts in the hematopoietic organs or the qualitative identity of the blood pictures from the presence of a peripheral macrocytosis.[42]

In the case of the blood from newborn rats, which Ivy and Higgins and their associates have used to study the effect of antianemic substances administered during gestation, there is a quantitative similarity to blood from patients with pernicious anemia, but qualitatively the two bloods are quite different. For example, in patients with pernicious anemia during relapse the percentage of reticulocytes is generally less than normal. These are almost exclusively products of the megaloblastic series and represent reticulated megalocytes. The macrocytosis in pernicious anemia is a megalocytosis which has resulted from the maturation of the pathologic megaloblastic series. On the other hand, in the blood of the newborn rat there are approximately 90 per cent or more reticulocytes.[12] When the sites of origin, conditions under which the cells are formed and the types of cellular precursors are considered, the macro-

39. Dameshek, W., and Valentine, E. H.: The Sternal Marrow in Pernicious Anemia: Correlation of the Observations at Biopsy with the Blood Picture and the Effects of Specific Treatment in Megaloblastic ("Liver-Deficient") Hyperplasia, Arch. Path. **23**:159 (Feb.) 1937.

40. Aron, M.: L'origine du sang dans le foie embryonnaire chez les mammifères, Arch. de morphol. gén. et expér., 1922, no. 10. Zanaty, A. F.: Erythrokonten und Erythropoese bei der Biermerschen Anämie und bei den Embryonen, Virchows Arch. f. path. Anat. **293**:794, 1934.

41. Benhamou, E.: Le traitment des anémies macrocytiques nou biermériennes, Presse méd. **47**:755 (May 17) 1939. Limarzi, L. R.: Diagnostic Value of Sternal Marrow Aspirations, Illinois M. J. **75**:38 (Jan.) 1939. Markoff, N.: Erythropoetische Knochenmarksfunction bei Lebercirrhose und Hämochromatose, Deutsches Arch. f. klin. Med. **183**:289 (Aug.) 1938. Revol, L.: L'exploration de la moelle osseuse par pounction sternale, Paris, J. B. Bailliere et fils, 1938. Rohr.[28]

42. (*a*) Davidson, L. S. P.: The Mechanism of Megaloblastic Blood Formation, Edinburgh M. J. **46**:474 (July) 1939. (*b*) Israels, M. Ç. G.: The Pathological Significance of the Megaloblast, J. Path. & Bact. **49**:231 (July) 1939.

cytosis in the blood of the newborn rat is qualitatively different from that in pernicious anemia. The newborn rat has some cells circulating in its blood which are the end products of those originally formed intravascularly in the yolk sac during the prehepatic period, large erythrocytes which are the products of large normoblasts formed extravascularly in the liver and erythrocytes formed from smaller normoblasts in the bone marrow, to say nothing of the spleen. Not only have all of these nonnucleated corpuscles been formed in different hematopoietic sites, but there is some evidence to indicate that their hemoglobins may differ.[43] If the antianemic principle which is effective in reducing the cell size in pernicious anemia does influence the blood picture of the newborn rat, it would be difficult to understand the actual mechanism involved in producing this reduction of cell size in the newborn rat. For example, the active agent might accelerate the erythropoiesis in the yolk sac; definitive, or normoblastic, cells might appear precociously; the size of cells formed in the liver might be decreased or erythropoiesis in the bone marrow and spleen might be stimulated.

MATERIAL AND METHODS

The pregnant rats, from which the 11 day embryos were obtained, originated from a strain of Wistar Norwegian white rats. The colony diet consisted of Purina dog chow (checkers)[43a] supplemented by fresh green food biweekly. Females in the proper stage of estrus were each placed with a male shortly after midnight. The following morning at 9:30 a. m. vaginal smears were examined for the presence of sperm cells. If the latter were present, then this was taken as the starting point for timing the age of the embroys in days. Pregnant rats were placed in wire cages provided with feeding cups so constructed that the food could not be scratched out. Diets containing various percentages of desiccated stomach were made by using uniformly ground Purina dog chow (checkers) as a base to which 20 per cent by weight of ventriculin N. N. R. or ventriculin concentrate[43b] was added. Other diets containing 10.0, 5.0, 2.5, 1.25 and 0.625 per cent, respectively, were made by attenuating the 20 per cent mixture.

All rats were killed by ether between 9:30 and 10:00 a. m. on the desired day of gestation. Since blood in the early stages of embryonic development does not lend itself readily to investigation by means of dry smears, the method of making dry smears of the yolk sac originally described by Kirschbaum[44] was utilized.

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43. Brinkman, R., and Jonxis, J. H. P.: Occurrence of Several Kinds of Haemoglobin in Human Blood, J. Physiol. **85**:117 (Oct. 26) 1935.

43a. Purina dog chow (checkers) contains 21 per cent crude protein; 4 per cent crude fat; 6 per cent crude fiber and 46 per cent nitrogen-free extract. The ingredients are meat meal, dried skimmed milk, wheat germ, barley malt, dried beet pulp, corn grits, corn and wheat cereal feed, dried raisins, soy bean oil meal, molasses, riboflavin concentrate, carotene, dried brewers' yeast, cod liver oil, 1 per cent steamed bone meal and iodized salt.

43b. Ventriculin concentrate was obtained from Parke, Davis & Co.

44. Kirschbaum (footnotes 16*f* and *g*). Kirschbaum, A., and Downey, H.: A Comparison of Some of the Methods Used in Studies of Hemopoietic Tissues, Anat. Rec. **68**:227 (May) 1937.

The best preparations were obtained from the thinnest smears. Although it is desirable to make preparations with little or no maternal blood from the placenta, for practical purposes its presence is not a serious handicap, since embryonic cells cannot be confused with any of the cells in the maternal circulation. In a similar manner preparations with or without supravital and vital dyes were made for studying the living cells. Some embryonic vesicles were also fixed in Zenker's stock solution to which was added solution of formaldehyde U. S. P. (9:1), embedded in pyroxylin and stained with hematoxylin azure II and eosin.

Emphasis must be placed on the fact that the embryos implanted near the tubal extremity of the uterus are slightly more advanced in development than those near the cervix.[45] According to Mossman, this difference in development is roughly progressive from the one end of the uterine horn to the other. Hence, in sampling material for quantitative studies it is of the utmost importance that specimens are obtained from the tubal extremity of the uterus to the cervix and from each side. It should be pointed out at this time that the great variation in the physiologic macrocytosis within a given litter of newborn rats is due not to differences in the amount of antianemic principle available to each fetus from day to day, as suggested by Stasney, Higgins and Mann,[6c] but to the difference in the length of time of implantation.[45a]

In the present study, 100 cells and nuclei were measured from the yolk sac blood of at least 5 embryos. If more than one smear was made from a given yolk sac, then an equal number of cells and nuclei were measured from each. This was accomplished by using a slight modification of the Price-Jones method,[46] which consisted in outlining the cells and nuclei with a 6 H pencil by means of a camera lucida at a magnification of 1,000. Only cells from the thinnest portion of the smears were drawn. Care was exercised that well preserved, isolated, intact and properly flattened cells were drawn consecutively as they were encountered while the slide was being moved in an orderly fashion. The cell and nuclear outlines were measured with a glass millimeter scale graduated to 0.5 micron. The maximum and the minimum diameter through the center of the cell or nucleus were measured to 0.5 micron, and the mean of these two measurements was determined. The control series of mean cell and nuclear diameters was obtained by measuring 200 cells in the yolk sac blood from each of 28 embryos from 5 pregnant rats.[47] This series could not be used in the present quantitative study because there were differences in the time of mating the rats, their diets and the method of sampling blood from the embryos.

OBSERVATIONS

In the first series of experiments pregnant rats were fed diets containing 20 per cent by weight of desiccated stomach preparation because this diet was the one originally reported by Briese and Higgins.[7a] Two

45. Mossman, H. W.: Comparative Morphogenesis of the Fetal Membranes and Accessory Uterine Structures, Contrib. Embryol. **26**:129 (Jan.) 1937.

45a. Jones, O. P.: The Degree of Macrocytosis in Blood from Newborn Rats as Related to the Time of Implantation, Anat. Rec. **79** (supp. 3):35 (March 25) 1941.

46. Price-Jones, C.: Red Blood Cell Diameters, London, Oxford University Press, 1933.

47. An additional control series of 5,000 cells from 14 embryos obtained from 9 pregnant rats (University of Minnesota stock) was used as a qualitative check.

rats (experiments 1 and 2) received ventriculin concentrate [47a] in their diets, and 6 rats (experiments 13 to 18) received regular ventriculin, or ventriculin N. N. R. When the mean cell and nuclear diameters had been calculated the results were found to be surprisingly unlike those

*Summary of Experimental Data**

Experiment No.	Rat No.	Body Weight, Kg.	Diet, Percentage of Ventriculin by Weight	Average Daily Dose Ventriculin, Gm.	Daily Dose Ventriculin, Gm. per Kg.	Mean Cell Diameter, Microns	Standard Deviation, Sigma (σ)	Critical Ratio	Mean Nuclear Diameter, Microns	Standard Deviation, Sigma (σ)	Critical Ratio
					Control						
	....	.....	....	....	....	14.44	1.42	....	9.29	1.01	....
					Ventriculin Concentrate						
1	37B	0.302	20.0	3.43	11.4	14.42	1.39	0.4	**9.14**	0.96	**3.3**
2	41B	0.205	20.0	3.21	15.7	**14.25**	1.27	**2.2**	9.44	0.96	3.3
3	33B	0.219	10.0	1.62	7.4	**13.72**	1.36	**11.4**	**8.79**	0.94	**11.2**
4	70B	0.217	10.0	1.50	6.9	**14.23**	1.44	**3.1**	**9.09**	1.08	**4.1**
5	38B	0.219	5.0	0.78	3.6	14.35	1.40	1.6	9.25	0.98	0.8
6	44B	0.218	5.0	0.88	4.0	14.5	1.42	1.1	9.21	1.01	1.6
7	57B	0.263	2.5	0.45	1.7	**13.75**	1.30	**11.4**	**8.88**	0.91	**9.6**
8	54B	0.251	2.5	0.31	1.3	**13.94**	1.34	**8.0**	**8.79**	0.91	**11.6**
9	102	0.252	1.5	0.21	0.81	**14.27**	1.33	**2.8**	**9.06**	0.95	**5.0**
10	58B	0.200	1.25	0.18	0.89	**13.89**	1.35	**11.9**	**8.72**	0.99	**12.2**
11	60B	0.504	0.625	0.10	0.38	**13.86**	1.41	**8.8**	9.21	0.95	1.9
12	63B	0.253	0.625	0.10	0.39	14.55	1.43	1.5	9.61	1.01	6.6
					Ventriculin N. N. R.						
13	34B	0.252	20.0	2.89	11.5	14.49	1.37	0.7	9.20	0.90	2.3
14	35B	0.277	20.0	3.66	13.2	14.43	1.54	0.3	9.73	1.12	8.5
15	39B	0.195	20.0	2.64	13.5	14.42	1.38	0.4	9.35	0.98	1.3
16	71B	0.222	20.0	3.29	14.8	14.84	1.67	5.3	9.55	1.14	5.0
17	73B	0.231	20.0	2.67	11.6	14.72	1.65	3.7	9.61	1.11	6.3
18	91B	0.247	20.0	3.30	13.3	14.87	1.65	5.6	9.36	0.98	1.5
19	69B	0.217	10.0	1.49	6.9	**14.06**	1.31	**0.3**	**9.08**	0.85	**4.9**
20	94B	0.179	5.0	0.87	4.9	14.34	1.50	1.5	**9.05**	0.99	**5.2**
21	95B	0.211	5.0	0.90	4.3	14.36	1.45	1.2	9.31	1.00	0.4
22	160	0.261	5.0	0.75	2.8	14.48	1.44	0.6	**9.07**	0.96	**4.9**
23	153	0.236	2.5	0.44	1.8	**14.12**	1.38	**5.0**	**9.07**	0.89	**5.3**
24	59B	0.291	2.5	0.52	1.8	**13.42**	1.22	**17.6**	**8.81**	1.00	**10.2**
25	75B	0.279	1.25	0.25	0.89	**14.19**	1.32	**4.0**	**8.88**	0.86	**10.3**
26	72B	0.202	1.25	0.19	0.96	**13.95**	1.37	**7.9**	**9.16**	0.99	**2.9**
27	49B	0.290	0.625	0.11	0.37	14.31	1.43	2.4	**9.01**	1.03	**5.8**
28	66B	0.192	0.625	0.10	0.50	**14.13**	1.46	**4.6**	9.16	1.11	2.5
					Ventriculin and Liver Extract						
29	68B	0.190	20.0	2.18	11.5	14.41	1.43	0.6	9.19	0.96	2.2
30	74B	0.197	20.0	2.40	12.2	**14.25**	1.37	**3.0**	**8.97**	1.02	**6.8**

* The figures set in bold-faced type indicate the mean diameters which were significantly decreased from the normal mean and their critical ratios.

anticipated from the work of Briese and Higgins.[7a] Data in the table show that neither the cell nor the nuclear diameters of the embryonic blood cells were significantly decreased by the diets containing regular

47a. The ventriculin concentrate was obtained in the form of B 924959, from Parke, Davis & Co. This preparation is three to four times more effective than ventriculin N. N. R. as measured by the daily dose required for induction of remission in a case of severe relapse of pernicious anemia.

ventriculin. There was, however, a slight but significant change in these diameters when the diets contained 20 per cent ventriculin concentrate.

In order to compare the daily dosage of stomach preparation fed to the pregnant rats with that administered during relapse to patients with pernicious anemia, it was considered more accurate to use the mean body weight of the latter group than a mean of the body weight of normal adult human beings.. Dr. Raphael Isaacs furnished this information from the records of the Simpson Memorial Institute, Ann Arbor, Mich. The arithmetic mean of the body weight of 500 patients was 133.58 pounds, or 63 Kg. Since regular ventriculin is standardized so that the daily oral administration of 30 Gm. will induce a remission, this value was selected as the maximum human dose. In this case the average human dose is 0.48 Gm. per kilogram of body weight. It is obvious from data in the table that pregnant rats which were fed diets containing 20 per cent ventriculin, as reported by Briese and Higgins,[7a] were receiving twenty-three to thirty times the maximal human per kilogram daily dose. Although it was known that such a nonphysiologic diet might be causing the loose stools and diarrhea present in most of these rats, the exact relation of these two factors with the lack of a decrease in the diameters of embryonic blood cells was not recognized at this time. Data in the table show that there was a significant decrease in both the cell and the nuclear diameters of blood cells from embryos from pregnant rats (experiments 3, 4 and 19) fed diets containing 10 per cent ventriculin or ventriculin concentrate. These changes with the 10 per cent mixtures were so constant and significant that diets containing smaller quantities of desiccated stomach were tried. The table shows that a significant change in either the cell and/or the nuclear diameters was obtained when the diets contained 5.0, 2.5, 1.5, 1.25 and 0.625 per cent desiccated stomach. Lesser concentrations were not tried because the last-named amount appeared to be a suboptimal quantity. It will be noted that embryos from rats in experiments 5 and 6, which were fed a diet with 5 per cent ventriculin concentrate, did not have a significant change in the size of blood cells. This may be partly accounted for on the basis of inadequate and faulty sampling, which was due to the accidental bursting of embryonic vesicles from the tubal extremity of the uterus, thereby making it impossible to get a good series of representative preparations.

Data in the table and figure 1 show that as a rule diets containing the lesser quantities of gastric preparation influenced embryonic erythropoiesis more efficaciously than those containing higher concentrations. This is further emphasized in the following experiments, the results of which are shown in figure 2. Litter mate rats (experiments 16 and 26) were successfully bred on the same night. The following

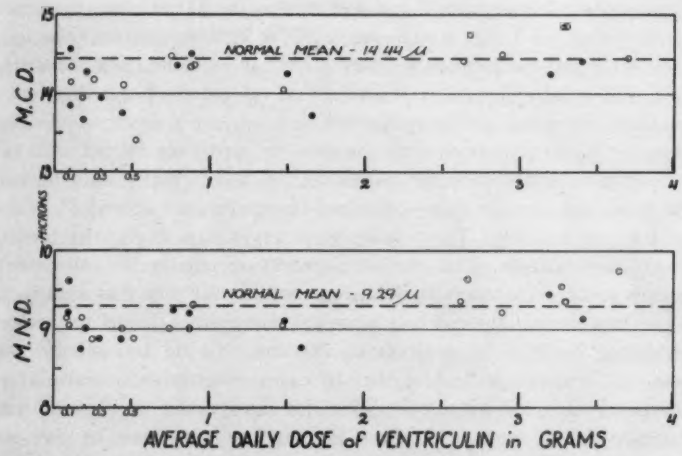

Fig. 1.—The circles represent the mean diameter of cells (*M.C.D.*) and nuclei (*M.N.D.*) of blood obtained from embryos from pregnant rats fed diets containing ventriculin. The dots represent the mean diameters of blood cells from embryos from pregnant rats receiving ventriculin concentrate.

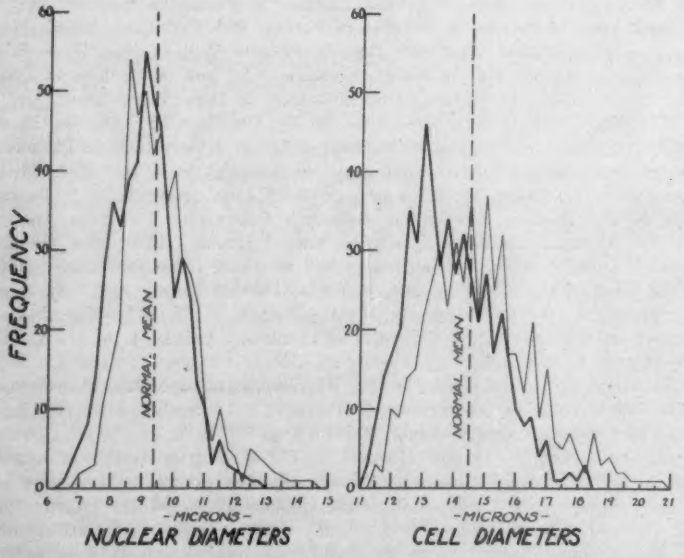

Fig. 2.—The heavy line represents the diameter of blood cells from embryos from a pregnant rat (72 B) fed a 1.25 per cent ventriculin diet. The thin line shows the diameters of cells obtained from blood of embryos from a pregnant rat (71 B) fed a 20 per cent ventriculin diet.

morning one rat was started on a diet containing 20 per cent ventriculin and the other on a diet containing 1.25 per cent ventriculin. The data in the table and the frequency distribution curves of figure 2 show that blood cells from embryos from a pregnant rat fed the latter diet had a significant decrease in the mean cell and nuclear diameters. Similar values for blood cells from embryos from the pregnant rat fed a 20 per cent ventriculin diet were not decreased, but were greater than normal. The same type of reaction was obtained in experiments 18 and 25, which also ran concurrently. These differences might have been attributed to the injurious effects of an excessive amonut of antianemic substance [48] on embryonic erythropoiesis if it were not for the fact that rats fed a 20 per cent ventriculin diet had some gastrointestinal disturbance which manifested itself as loose stools or diarrhea. Castle and others have presented evidence indicating that in cases of macrocytic anemia the absorptive capacity of the intestine for antianemic substances may gradually fail [49] even until there is complete resistance to the oral administration of liver extract [50]; it may be diminished by obstruction, intestinal anastomoses [51] and acid mixtures of intrinsic and extrinsic

48. Minot, G. R.: Some Fundamental Clinical Aspects of Deficiencies, Ann. Int. Med. **3**:216 (Sept.) 1929.

49. (*a*) Castle, W. B.; Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: IV. A Biologic Assay of the Gastric Secretion of Patients with Pernicious Anemia Having Free Hydrochloric Acid and That of Patients Without Anemia or With Hypochromic Anemia Having No Hydrochloric Acid, and of the Rôle of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, Am. J. M. Sc. **182**:741 (Dec.) 1931. (*b*) Castle, W. B.; Rhoads, C. P.; Lawson, H. A., and Payne, G. C.: Etiology and Treatment of Sprue: Observations on Patients in Puerto Rico and Subsequent Experiments on Animals, Arch. Int. Med. **56**:627 (Oct.) 1935. (*c*) Castle, W. B.; Townsend, W. C., and Heath, C. W.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: III. The Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding, Am. J. M. Sc. **180**:305 (Sept.) 1930. (*d*) Isaacs, R.; Sturgis, C. C.; Goldhamer, S. M., and Bethell, F. H.: The Use of Liver Extract Intravenously in the Treatment of Pernicious Anemia, J. A. M. A. **100**: 629 (March 4) 1933.

50. Minot, G. R., and Castle, W. B.: The Interpretation of Reticulocyte Reactions: Their Value in Determining the Potency of Therapeutic Materials, Especially in Pernicious Anemia, Lancet **2**:319 (Aug. 10) 1935.

51. (*a*) Barker, W. H., and Hummel, L. E.: Macrocytic Anemia in Association with Intestinal Strictures and Anastomoses: Review of the Literature and Report of Two New Cases, Bull. Johns Hopkins Hosp. **64**:215 (April) 1939. (*b*) Castle, Heath and Strauss.[49a] (*c*) Little, W. D.; Zerfas, L. D., and Trusler, H. M.: Chronic Obstruction of the Small Bowel the Result of Two Entero-Enterostomies and Apparently the Cause of Pernicious Anemia, J. A. M. A. **93**: 1290 (Oct. 26) 1929.

factors,[52] and, finally it may be altered by diarrhea [53] or changes in the intestinal wall itself.[49b] However, Barker and Rhoads [54] expressed the belief that malabsorption in patients with sprue results in diarrhea, and is not produced by it. In addition to malabsorption of antianemic substance, that of the carbohydrates [55] and fats [54] has also been reported.

The fact that a 20 per cent ventriculin diet was ineffective whereas a 1.25 per cent ventriculin diet stimulated embryonic erythropoiesis, has a counterpart in the case report by Isaacs and associates.[49d] The essence of the report is that a man aged 22 with a history of pernicious anemia beginning four years previously did not respond to administration of desiccated hog stomach in doses up to 150 Gm. daily. During a subsequent relapse he was given 40 to 50 Gm. of desiccated hog stomach, which produced a markedly submaximal response. Since this patient responded early in the course of his disease to the juice from 1 to 3 pounds (453 to 1,306 Gm.) of liver a day and later gave only a submaximal response to 40 to 50 Gm. of stomach preparation, it might be assumed that this was caused by a progressive development of defective absorption of hematopoietic substances.[49] In view of the negative results obtained when pregnant rats were fed diets rich in ventriculin, it might also be that the patient of Isaacs and associates [49d] did not respond to the dose of 150 Gm. of stomach preparation daily because of the changes produced in the intestinal wall due to the massive doses of the preparation.

In the rat these changes consisted of a decreased number of goblet cells and an increase of lymphoid cells in the lamina propria of the cores of villi. These cells were chiefly small and medium-sized lymphocytes and polyblasts. In some sections the number of globular leukocytes was striking. Because the material was stained only with hematoxylin-triosin after fixation in Bouin's fluid, it was impossible to determine whether the high ventriculin diet caused the transformation of polyblasts into basophil myelocytes, which has been reported in guinea pigs after subcutaneous injection of autoclaved ventriculin (a 5 per cent suspension in Tyrode solution without sodium bicarbonate).[56] Furthermore, it was

52. Castle, W. B.; Heath, C. W.; Strauss, M. B., and Heinle, R. W.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: VI. The Site of the Interaction of Food (Extrinsic) and Gastric (Intrinsic) Factors; Failure of in Vitro Incubation to Produce a Thermostable Hematopoietic Principle, Am. J. M. Sc. **194**:618 (Nov.) 1937.

53. Castle, Heath and Strauss.[49a] Castle, Rhoads, Lawson and Payne.[49b]

54. Barker, W. H., and Rhoads, C. P.: The Effect of Liver Extract on the Absorption of Fat in Sprue, Am. J. M. Sc. **194**:804 (Dec.) 1937.

55. Hanes, F. M., and McBryde, A.: Identity of Sprue, Nontropical Sprue and Celiac Disease, Arch. Int. Med. **58**:1 (July) 1936.

56. Plimpton, N. C.: Basophil Leucocytes and Myelocytes After Local Injection of Ventriculin, Anat. Rec. **76**:475 (April) 1940.

also impossible to determine whether this type of diet would cause the argentaffine cells to increase, as implied in the recent work by Jacobson.[57]

Castle and Ham [58] have schematically represented the factors which are concerned with the production of the antianemic principle: $\frac{F \times G}{I}$ = L.E. In this formula, F stands for food (extrinsic) factor, G for gastric (intrinsic) factor, I for intestinal impermeability and L.E for liver extract. A similar scheme can be used to represent the relation of the several factors concerned with the absorption of some antianemic substance from the maternal gastrointestinal tract and its subsequent influence on embryonic erythropoiesis. Instead of expressing intestinal absorption in terms of impermeability (I), for the sake of clarity I find it is more appropriate to let I equal $\frac{1}{P}$, P standing for intestinal permeability. In this case Castle and Ham's equation can be expressed as L.E. equals $F \times G \times P$. Furthermore, if a reduction in the mean cell and nuclear diameters of the primitive erythroblasts of embryonic blood is used to indicate the effectiveness of some antianemic substance absorbed from the maternal gastrointestinal tract and transmitted across the placenta, then it should follow that L.E. equals $\frac{1}{M.D.}$, M.D. being mean diameter. It is, of course, understood that the L.E. of Castle and Ham's equation is not necessarily identical with the antianemic substance acting on the embryonic blood cells, but both substances do have the property of reducing cell size. Substituting these values in the original equation, then M.D. = $\frac{1}{F \times G \times P}$. When normal pregnant rats are fed diets containing ventriculin, the factor $(F \times G)$ is constant for any one animal during the experiment, since the antianemic activity of ventriculin depends on both the thermostable (extrinsic) and the thermolabile (intrinsic) factor.[58] If the factor $(F \times G)$ is increased, by feeding larger amounts of ventriculin, while M.D. remains the same or even increases, then the factor P must necessarily have decreased. Data in the table and in figures 1 and 2 indicate that some factor of intestinal permeability decreased with the higher concentrations of ventriculin after the maximum cell-reducing and nucleus-reducing effects have been obtained. In other words, $(F \times G)$ can be increased up to a certain point, with a resultant decrease in M.D., but beyond the maximum effective dose higher concentrations of ventriculin have little or no effect on the blood cells of the embryo because of the decreased permeability

57. Jacobson, W.: The Argentaffine Cells and Pernicious Anaemia, J. Path. & Bact. **49**:1 (July) 1939.

58. Castle, W. B., and Ham, T. H.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: V. Further Evidence for the Essential Participation of Extrinsic Factor in Hematopoietic Responses to Mixtures of Beef Muscle and Gastric Juice and to Hog Stomach Mucosa, J. A. M. A. **107**:1456 (Oct. 31) 1936.

produced by such a diet. Data in the table also indicate that the mean diameters of embryonic blood from rats in experiments 16 to 18 were significantly increased from the normal mean. This might be interpreted to indicate that factor P was decreased to such an extent that the mother was not even absorbing amounts of food and antianemic substance necessary for normal embryonic erythropoiesis in spite of a superabundance of ventriculin in the diet.

It is known that intestinal permeability may be markedly influenced by increased peristalsis and diarrhea, with a resultant malabsorption of substances from the intestine.[59] It should, therefore, be possible to predict a priori (according to the aforementioned equations) whether maximal or minimal changes are to be expected in a given experiment by observing the consistency of the stools. Experiments 20 and 21 ran concurrently, and it was noted that the rat in the latter experiment had stools which were loose as compared with those of the rat in the former experiment, which were quite normal. Before the termination of these experiments it was anticipated that the blood cells from the embryos from the rat with the loose stools would not be decreased to the same extent as those in the other experiment. Data in the table show that the nuclear diameters were significantly decreased in experiment 20, whereas the cell and nuclear diameters remained unaltered in experiment 21. In experiments 22 and 23, which also ran concurrently, it was anticipated that the changes in the former would not be maximal, since the rat had soft stools. Data in the table support this supposition. In experiment 9 the changes in the mean diameters were not as great as those in experiments 8 and 10, and the rat in this experiment also had slightly loose stools. It will be noted that the gastrointestinal tract of rats fed identical diets reacted differently. In the case of rats which were fed 20 per cent regular ventriculin (experiments 13 to 18) it is significant that the trend of the mean diameters was constantly normal or greater than normal and that in most of these animals the diarrhea was pronounced.

It might be argued that a diet containing 20 per cent ventriculin fed to pregnant rats has no influence on erythropoiesis in the 11 day rat embryo because of its deleterious effect on the placenta rather than its malabsorption from the intestine (fig. 3). On the other hand, if a barrier has been created in the maternal intestinal wall by a diet containing 20 to 30 times the maximal human per kilogram daily dose of desiccated stomach, then the placenta should be unaffected and transmit antianemic substances administered through another route—the intramuscular. The

59. Castle, Heath and Strauss.[49a] Castle, Rhoads, Lawson and Payne.[49b] Davidson.[42a]

following experiments were devised to test these two points. Pregnant rats (experiments 17, 29 and 30) were fed a 20 per cent ventriculin diet, which previous experiments have demonstrated to be ineffective in influencing embryonic erythropoiesis in spite of the superabundance of antianemic substance in the maternal gastrointestinal tract. This diet was continued throughout the first eleven days of pregnancy. On the seventh, eighth, ninth and tenth days of pregnancy the rat in experiment 29 was given an intramuscular injection of 1 cc. of concentrated liver extract.[59a] The reasons for administering liver extract intramuscularly on these particular days were twofold. First, it was thought that after the rat had consumed the 20 per cent ventriculin diet for a week intestinal malabsorption should be well established. Second, the seventh to tenth days of pregnancy are before and during the first period of embryonic erythropoiesis.[16d] At the same time another pregnant rat (experiment 17) was fed the 20 per cent ventriculin diet, but it did not receive liver extract intramuscularly. Data in the table show that although the mean cell and nuclear diameters of blood cells from embryos out of the rat

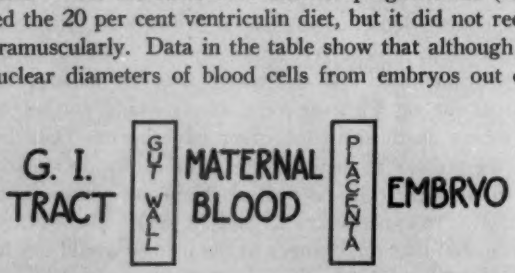

Fig. 3.—A schematic representation of the barriers antianemic substance must cross in a pregnant animal before it can influence embryonic erythropoiesis.

in experiment 29 which received ventriculin and liver extract were much less than those in the embryos from the rat in experiment 17, they were not significantly shifted from the normal mean. However, the nuclear size did show a trend in the direction of reduction. These negative results were not interpreted to indicate a faulty placental barrier, since the liver extract was not a regular clinically tested and approved product and the animal did not tolerate well such a massive dose. These massive, nonphysiologic doses of liver extract were used because the amount metabolized and excreted by the mother is unknown, the degree of placental permeability to antianemic substances is unknown and, if the placenta is permeable, at least a dozen embryos have to have an amount sufficient to be effective. Finally, large doses of antianemic substances might cause the precocious appearance of normoblasts. Rat 74 B was treated in the same manner, except that it received intra-

59a. The concentrated liver extract was obtained from Parke, Davis & Co. for investigational purposes only.

muscularly 2 cc. of regular liver extract [59b] on the seventh and ninth days of gestation. Data in the table show that both the mean cell and the nuclear diameter of the embryonic blood cells were significantly decreased from the normal mean. When these values are plotted against a frequency distribution curve of the cell and nuclear diameters of blood from all embryos from rats fed a diet of 20 per cent ventriculin (fig. 4), it is evident that some antianemic substance from the liver extract given intramuscularly must have been transmitted across the placenta, which was still permeable. The latter fact agrees with the results obtained in previous experiments.[16d] It has been pointed out by Barker and asso-

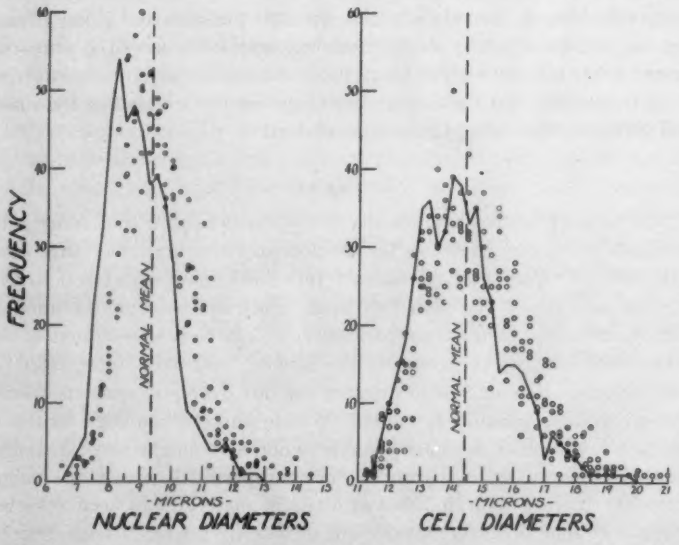

Fig. 4.—The circles represent the diameters of blood cells from all embryos from pregnant rats (experiments 13 to 18) fed a 20 per cent ventriculin diet. The solid line indicates the diameters of blood cells from embryos from a pregnant rat (experiment 30) receiving a 20 per cent ventriculin diet and parenteral injections of liver extract on the seventh and ninth days of gestation.

ciates [60] that injections of liver extract may increase the permeability of the intestine for certain food substances in some macrocytic anemias. If this condition obtains for the normal pregnant rat in experiment 30 fed a diet of 20 per cent ventriculin and given injections of liver extract,

59b. The regular liver extract was obtained in the form of liver extract (intramuscular)—Parke, Davis & Co.

60. Barker and Hummel.[51a] Barker and Rhoads.[54]

then it would be difficult to ascertain how much of the cell-reducing effect was produced by the liver extract given intramuscularly and how much by the antianemic substance absorbed from the gastrointestinal tract after the permeability had been increased. In view of the relatively short time elapsing between the injections of liver extract and the termination of the experiment, and of the fact that intramuscular injections of liver extract alone will produce similar changes,[16d] the effect on embryonic erythropoiesis is perhaps for the most part due to something in this substance. These experiments indicate that high concentrations of ventriculin are ineffective because of a barrier which has been created in the intestinal wall and that the placenta will transmit antianemic substance providing it is made available through the maternal blood stream (fig. 3). Even if loose stools, diarrhea and mild enteritis were not present in the rats fed high concentrations of ventriculin, one would arrive at the conclusion that there is a physiologic barrier created in the intestinal wall and that the placenta is unaffected.

COMMENT

The present studies are not the first to demonstrate that some antianemic principle can accelerate the development of primitive erythroblasts in the embryo. Cohn and associates [61] furnished Sabin with fraction R of liver extract, which she added to living chick blastoderms mounted in Locke's solution. In these preparations mitoses were accelerated in the endothelium and in the cells which Sabin [18] originally interpreted as megaloblasts. Reimer,[62] who injected various liver preparations diluted with physiologic solution of sodium chloride into chicken eggs incubated for three to seventeen days, was unable to find any qualitative or quantitative changes in the blood. He did observe nonspecific degenerative changes in the liver, which indicated that at least the material had been absorbed by the embryo. However, the present studies are the first to demonstrate that primitive erythroblasts of mammalian embryos can be influenced by some antianemic substance transmitted across the placenta.[63] The observations by Sabin,[61] cited by Cohn and associates, and the results of the present study support the concept that some antianemic substance acts directly on the primitive red cells, perhaps by supplying a building stone for their proper maturation. In contrast to this, Barker and Hummel [51a] have made some interesting tentative assumptions regarding the possible

61. Cohn, E. J.; Minot, G. R.; Alles, G. A., and Salter, W. T.: The Nature of the Material in Liver Effective in Pernicious Anemia: II., J. Biol. Chem. **77**: 325 (May) 1928.

62. Reimer, L.: Versuche zur Beeinflussung der Blutbildung beim Hühnerembryo durch Antiperniciosastoff, Arch. f. exper. Path. u. Pharmakol. **189**:656, 1938.

63. Jones (footnotes 16*d* and *e*).

action of liver principle in treatment of macrocytic anemia. For example, they claimed that the active principle might act on a normally functioning liver and promote the detoxification of injurious substances which had prevented normal erythropoiesis. The studies of both Sabin, cited by Cohn and associates,[61] and Jones [63] on the influence of antianemic substances before and during the prehepatic period of embryonic development certainly would indicate that this principle can exert its influence in the absence of a functioning liver. If the assumption made by Barker and Hummel [51a] is correct, then prehepatic embryonic erythropoiesis, which stimulates, but is not identical with, that in pernicious anemia, is due to the absence of detoxifying powers normally possessed by the liver.

Although the results in the present study seem to contradict those reported by Briese and Higgins,[7a] it must be borne in mind that the two experiments are quite different with respect to the duration of the experiment and nature of the blood cells measured. It is not unlikely that the intestinal impermeability created by diets of 20 per cent ventriculin during the first eleven days of pregnancy might break down when the rats are fed this diet throughout the entire period of gestation. And, then, other sites of erythropoiesis, such as the liver, the spleen and the bone marrow, may be more labile in their response than the yolk sac. In the present report the decrease in cell and nuclear diameters is due to an acceleration of cytoplasmic differentiation and nuclear maturation of the primitive erythroblasts. It has been mentioned in the first part of this paper that the decrease in the size of blood corpuscles from newborn rats reported by Briese and Higgins [7a] is difficult to analyze, since the yolk sac, liver, spleen and bone marrow may not respond alike and to the same degree. The results obtained by Briese and Higgins [7a] may be due to stimulation of erythropoietic foci of normoblasts (definitive erythroblasts).

Also, it should be strongly emphasized that so far it has been impossible to cause a transformation of primitive erythroblasts (Sabin's megaloblasts)[18] into normoblasts or cells of the definitive series.[63] This is based on a consideration of cell size, nucleocytoplasmic ratio and nuclear structure. This lends some support to the view held by those who have maintained that the megaloblasts occurring in pernicious anemia complete their maturation as megalocytes and are not transformed into cells of the normoblastic series after antianemic therapy.[64]

If a decrease in the mean diameters of embryonic blood cells is used to indicate the effectiveness of antianemic substance absorbed from the maternal gastrointestinal tract, then, according to data in the table, impermeability of the intestinal tract to antianemic substance did not commence to increase appreciably until the rats were fed a daily dose of

64. Bock and Malamos.[26] Fieschi.[27] Jones.[27a] Naegeli.[24] Rohr.[28] Segerdahl.[29] Storti.[30]

ventriculin equivalent to 6 Gm. per kilogram of body weight. This is roughly twelve times the human dose per kilogram of body weight. In the case reported by Isaacs and associates,[49d] the patient did not respond even after receiving a daily dose five times the usual maximum human dose. This increased malabsorption in the human subject may be due to the gradual failure of the absorptive capacity of the intestine for antianemic substances in macrocytic anemias.[65] Or it may be due to changes produced in the intestinal wall by the drug itself. In the rat the intestinal impermeability does not make its appearance until at least three times the maximal effective dose of ventriculin has been administered. Unfortunately, there are no data in the literature at present concerning how large a dose of desiccated hog stomach can be administered to a patient with pernicious anemia before malabsorption of this antianemic substance is set up by the mild enteritis.[66] It is also possible that the latter is produced in the pregnant rat and not in the human subject.

In view of the fact that slight excesses of antianemic substance in the diets of pregnant rats will accelerate embryonic erythropoiesis, it is of interest to note that Ritter and Crocker [67] reported a macrocytic anemia of pregnancy and an anemia of the newborn which were possibly due to the same dietary deficiency in the mother.

CONCLUSIONS

1. When normal pregnant rats are fed diets containing desiccated hog stomach, some antianemic substance absorbed from the gastrointestinal tract is transmitted across the placenta and influences prehepatic embryonic erythropoiesis.

2. Diets containing high concentrations of desiccated hog stomach are not as effective as those containing amounts nearer physiologic limits because of the increased intestinal malabsorption produced by the diet itself.

3. The effectiveness of antianemic substance after it has crossed the placenta is indicated by a reduction in the mean cell and nuclear diameters of the primitive erythroblasts of embryonic blood. In general, ventriculin concentrate is more effective than regular ventriculin.

4. On the basis of their nuclear pattern, cell size and nucleocytoplasmic ratio, cells of the first, or primitive, generation have not been trans-

65. Castle and others.[49] Minot and Castle.[50]

66. In a recent article Morrison has stated that intestinal permeability is an important and uncertain factor in determining the potency of oral preparations (Studies in Pernicious Anemia: An Inquiry into the Rôle of Pepsin, Ann. Int. Med. **14**:242 [Aug.] 1940).

67. Ritter, J. A., and Crocker, W. J.: Macrocytic Anemia of the Newborn, Am. J. Obst. & Gynec. **38**:239 (Aug.) 1939.

formed into cells of the second, or definitive, generation; however, their maturation has been accelerated.

NOTE.—After this manuscript was submitted for publication, two articles were published which seemed to nullify the interpretation of the foregoing results. This would be of great import if it were not for the fact that these two pieces of research are based on unsound premises. Last and Hays have reported that potent liver extract administered to pregnant rats did not increase the percentage of non-nucleated corpuscles in the blood of the 15 day rat fetus (Effect on Blood Picture of 15-Day Embryo of Liver Extract Injected into Pregnant Rats, Proc. Soc. Exper. Biol. & Med. **46:** 194 [Jan.] 1941). It does not necessarily follow that accelerated erythropoiesis in the 11 day embryo should be reflected in the blood on the fifteenth day by an increment of the non-nucleated corpuscles. Cytoplasmic differentiation and nuclear maturation do not proceed at the same rate. It is unfortunate that Last and Hays studied blood from 15 day fetuses, since slight, or even significant, changes in cells of the prehepatic generation are apt to be attenuated or completely masked by the rapidly growing normoblastic generation. This is the very thing which was specifically avoided in my studies of yolk sac blood from the 11 day embryo. Last and Hays have also reported that potent liver extract and ventriculin administered to pregnant rats "cannot" influence the maturation of primitive erythropoiesis of the 11 day rat embryo as determined by measuring the nuclear diameters (The Effect on the Blood Picture of the 11 Day Embryo of Liver Extract Injected into the Pregnant Rat, J. Pharmacol. & Exper. Therap. **72:** 25 [May] 1941). Here, again, it is unfortunate that these authors did not know that nuclear diameters are not decreased to the same degree as cell diameters after the administration of antianemic substances to the pregnant rat. Since the changes in cell diameters are more pronounced and since there is a greater percentage of error in measuring the smaller nuclear diameters, the latter have been completely discarded in my more recent studies. Although the quantitative changes seem small, there are certain qualitative changes which support my contention that there is a placental transfer of some antianemic principle. These will be reported on separately in the future.

Material was furnished by Dr. E. A. Sharp, of Parke, Davis & Co.; A. B. Constantine helped with the statistical analyses, and valuable personal communications were furnished by Dr. George M. Higgins, of the Mayo Clinic. The technical assistance furnished by R. Ament, A. B. Constantine and A. Seeger was made possible through the National Youth Administration.

STATE OF MOTOR CENTERS IN CIRCULATORY INSUFFICIENCY

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In a previous communication by an associate and us [1] the fusion frequency of flicker was reported as decreased in circulatory insufficiency (hypertension or heart disease). This decrease is probably due to a reduced oxygen supply to the central nervous system. Fatigue develops first in the sensory centers, and it spreads from there to involve other parts of the central nervous system. Visual centers are especially sensitive to the lack of oxygen. Hence the use of the fusion frequency of flicker might be expected to uncover changes not detectable by other methods. (For a review of pertinent literature, see the previous communication.[1])

The effect of fatigue on the motor centers has much practical significance, and its measurement is important, since, after all, "performance" is the objective clinical evidence of fatigue. Therefore, a combined investigation of a sensory and a motor function should enable us to come to some conclusions about the extent of the pathoiogic alterations in the central nervous system.

In order to obtain data directly comparable to those from investigations on the fusion frequency of flicker, we studied the maximum frequency of motor impulses.

As possibly the simplest method for determining the maximum frequency of motor impulses, we chose the measurement of the maximum frequency of finger movements. The findings of different authors [2]

From the Research Laboratories of Mount Sinai Hospital.

1. Simonson, E.; Blankstein, S., and Enzer, N.: The Fusion Frequency of Flicker in Circulatory Insufficiency, Ann. Int. Med., to be published.

2. Bruecke, F.: Die Nerven-Chronaxie als Funktion der Reizfrequenz, Arch. f. d. ges. Physiol. **233**:777, 1934. Raevsky, V. S., and Babdyanyane, M.: Influence du rythme du travail sur les changements de la chronaxie musculaire, Bull. biol. et méd. expér. URSS **5**:482, 1938. Lapicque, L.: Rapport de la chronaxie à la vitesse du mouvement dans divers tissus excitables, Compt. rend. Soc. de biol. **128**:688, 1938. Freeman, R. G., Jr., and Wechsler, D.: Note on the Correlation Between Chronaxie and Reaction Time, Proc. Soc. Exper. Biol. & Med. **29**:957, 1932. Latmanizova, L. F.: Chronaxie of Neuromuscular Apparatus in Conditions of Rhythmic and Non-Rhythmic Stimulation, Bull. biol. et méd. expér. URSS **6**:540, 1938. Hayasi, K., and Bruecke, E. T.: Ueber die Abhängigkeit der Nerven-Chronaxie von der Reizfrequenz, Arch. f. d. ges. Physiol. **235**:31, 1934.

indicate a close relation between chronaxia, the maximum frequency of discharge of the motor centers, and the speed or frequency of movements. As the weight of the fingers, and consequently the inertia in finger movements, is small, the relation between the maximum frequency of finger movements and the maximum frequency of the actual number of motor impulses is close. Lehmann [3] has shown that the number of motor impulses is directly proportional to the speed of finger movements. The actual frequency of motor impulses in voluntary movements is higher than this method would reveal—according to the latest data of Bouman and van Rijnberk [4] about four to six times and according to the data of Simpson and Derbyshire [5] about one and a half times.

The performance of this test does not depend on any peripheral function; the increase of metabolic processes is slight; there is no demand for any considerable blood supply, and there are no such disagreeable sensations as characterize static work. The test measures function of the motor centers. The purpose of this study was to investigate the fundamental processes of fatigue and of adaptation of motor centers in circulatory insufficiency.

METHOD

The subject stood in front of a table on which an impulse counter was placed. He touched the button of the counter with his middle finger "as fast as possible." Before the recorded test the subject was given several trial tests in order to familiarize him with the technic. After that, he was asked to begin and to continue "until the stop signal," which was given after one minute. The number of contacts was registered each ten seconds by means of a stopwatch; thus, the values are expressed as the number of motor impulses per ten seconds.

The following values seem to be especially important: the maximum frequency, normally obtained in the beginning; the minimum frequency, to which the number of impulses drops during the test, and the difference between the maximum and the minimum frequency.

The test was repeated after a pause of one minute, in order to investigate the possible influence of adaptation. Comparison of the values of the first and the second performance could show a prevailing fatigue or a prevailing adaptation; in the first case the values of the second performance must be lower, and in the latter case higher, than those of the first performance. The test was performed first with the right hand and then with the left.

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3. Lehmann, G.: Ueber den Mechanismus bei Willkürbewegung, Arbeitsphysiol. **1**:1, 1928.

4. Bouman, H. D., and van Rijnberk, G.: On Muscle Sound Produced During Voluntary Contraction in Man, Arch. néerl. de physiol. **23**:34, 1938.

5. Simpson, H. N., and Derbyshire, A. J.: Electrical Activity of the Motor Cortex During Cerebral Anemia, Am. J. Physiol. **109**:99, 1934.

Values were obtained for 42 normal subjects from 20 to 64 years of age. Twenty-three patients with hypertension or heart disease were studied. In 19 of the patients the fusion frequency of flicker was measured.[1]

Patient	Age	Sex	Comment
1	26	F	Fully compensated mitral stenosis
2	17	F	Compensated mitral stenosis complicated by pregnancy
3	54	F	Hypertension, blood pressure 215/140; dyspnea; headache; occasional precordial pain
4	59	F	Hypertension, blood pressure 170/100; occasional severe dyspnea; heart enlarged to left
5	72	M	Hypertension, blood pressure 230/140; no cardiovascular symptoms
6	58	F	Hypertension, blood pressure 170/100; occasional precordial pain
7	33	F	Rheumatic heart disease; repeated decompensation and digitalization
8	52	M	Compensated mitral stenosis
9	66	M	Coronary occlusion; blood pressure 135/80; occasional precordial pain; dyspnea on exertion; controlled diabetes
10	62	M	Patient nervous; diagnosis not entirely clear; auricular fibrillation; old coronary occlusion
11	73	M	Chronic glomerulonephritis; left hydrothorax; edema of lower extremities; secondary cardiac decompensation
12	65	M	Moderate myocardial damage and premature ventricular contractions revealed by electrocardiogram; peculiar sound at area of mitral valve suggestive of ossification of valve
13	65	M	Edema of ankles and abdomen; dyspnea; fatigability; enlargement of heart to left; reduced renal function; auricular fibrillation and myocardial damage revealed by electrocardiogram
14	53	M	Mitral stenosis; symptoms of decompensation; attacks of unconsciousness
15	66	M	Hypertensive heart disease; tabetic form of dementia paralytica; blood pressure 220/130; heart enlarged to left; dyspnea on exertion
16	40	M	Pulmonary embolism 18 months ago; occasional dizziness; dyspnea on exertion; reduced working capacity; no objective cardiovascular findings
17	62	M	Coronary occlusion; severe pain in arms and hands; controlled diabetes
18	47	M	Myocardial damage revealed by electrocardiogram; no symptoms of decompensation; pain in left part of precordium
19	45	F	Hypertension, blood pressure 220/100
20	20	M	Hypertension, blood pressure 150/120; headache
21	54	M	Coronary sclerosis; bronchial asthma; possible myocardial damage revealed by electrocardiogram; dyspnea; palpitation; severe pain in left arm
22	70	M	Coronary arterial disease with pulmonary congestion; no angina
23	45	F	Hypertension, blood pressure 270/150, with palpitation and sometimes dizziness; digitalization

Normal subjects were found to have small daily variations. Hence a greater variation of the values in patients must be due to fluctuation in the state of the patients. Normal values decreased slightly with age. But this was true only for the statistical comparison of different age groups; single values overlapped. Thus, it was not necessary to take into consideration the ages of the patients in comparing their values with normal ones.

RESULTS

Since the values of the patients before the onset of disease are unknown, those determined in the present tests are classified in four categories, as follows: (1) decrease not probable, if the values are above the normal average; (2) decrease possible, if the values are between the normal average and the mean value of the normal average and the lowest normal limit; (3) decrease probable if the values are between

6. Footnote deleted by author.

the mean value and the lowest normal limit, and (4) pathologic decrease, if the values are below the lowest normal value. Only the fourth category is clearly defined; a pathologic decrease is proved if the patient's value is lower than the lowest of a sufficiently large number of normal subjects. All other categories are only approximate; a decrease, for instance, cannot be excluded even if the patient's value exceeds the normal average, but a decrease would not be probable in such a case.

Eight values were obtained by the repeated performance of the test: the maximum and minimum values for the right hand, first and second performances, and the corresponding values for two performances of the left hand. Table 1 shows the values of 42 normal subjects, the average, the lowest limit and the mean value determined by the

TABLE 1.—*Values of Motor Frequency (Impulses per Ten Seconds) of Forty-Two Normal Subjects*

Values	Right Hand				Left Hand			
	First Performance		Second Performance		First Performance		Second Performance	
	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum
Average (A).....	69.7	56.0	67.5	57.2	64.5	49.5	62.0	49.8
Lowest limit (L).....	60.0	45.0	55.0	49.0	55.0	40.0	50.0	39.0
Mean value (M)..... $\frac{A+L}{2}$	64.4	50.5	61.3	53.1	59.8	44.8	56.0	44.4

formula $\frac{A+L}{2}$, in which A = the normal average and L = the lowest normal value.

According to these normal standards, we arranged the patients' values in the four categories (table 2). The normal average, mean and lowest values are indicated by double lines. The absolute average, mean and lowest values are different for each of the eight maximum and minimum values; they are indicated in table 1.

Table 2 shows the values of the patients; each patient is identified by his number in the synopsis. Few values are in the category "decrease not probable." Most of the eight maximum and minimum values are below normal average. The maximum frequency of motor impulses is undoubtedly diminished in hypertension and in heart disease.

Most values of the patients lie below the lowest limit of normal, in the category "pathologic decrease." This is significant, for it shows that the method is able to reveal individual deviations as well as the reaction of the patients as a group in a statistical comparison with

TABLE 2.—*Values of Motor Impulse Frequency in Twenty-Three Patients with Hypertension or Heart Disease*

Patient No.	Right Hand				Left Hand				Classification
	First Performance		Second Performance		First Performance		Second Performance		
	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	
1	75	..	..	..	65	..	..	..	Decrease not probable
5	..	..	68	..	71	55	73	50	
7	70	56	..	..	..	..	..	..	
10	70	..	..	..	..	..	..	..	
11	..	..	..	..	..	..	..	50	
15	..	60	68	59	68	51	63	51	
16	..	..	..	..	..	59	..	..	
20	78	..	75	..	..	..	63	..	
									Normal average
1	..	55	65	56	..	48	58	48	Decrease possible
2	67	..	62	..	61	..	61	47	
4	..	..	..	..	..	..	..	48	
5	68	55	..	56	..	..	..	..	
7	..	..	65	54	60	..	57	..	
8	..	54	62	..	..	47	..	47	
10	..	..	..	..	..	..	57	..	
11	..	..	..	..	..	..	60	..	
15	68	..	..	..	..	..	..	..	
16	..	52	..	..	61	..	58	48	
18	65	..	..	..	..	..	..	45	
19	..	..	..	..	..	..	..	45	
20	..	58	..	..	66	..	..	47	
									Mean
2	..	49	..	52	..	47	..	..	Decrease probable
3	..	..	..	..	..	41	52	41	
4	63	..	59	..	..	44	55	..	
6	..	..	..	..	..	..	53	40	
7	..	..	..	..	..	44	..	43	
8	61	..	..	51	58	..	55	..	
9	..	45	..	..	..	..	50		
10	..	..	55	..	60	42	..	40	
11	..	47	..	..	..	..	..	..	
16	63	..	57	53	..	..	..	..	
17	..	..	..	..	..	..	..	40	
18	..	..	60	..	..	..	55	..	
19	..	47	..	..	..	43	52	..	
20	..	..	..	53	..	40	..	..	
22	..	..	..	..	..	..	..	39	
23	..	45	..	..	58	42	..	41	
									Lowest limit of normal
3	43	37	48	38	46	..	..	..	Pathologic decrease
4	..	39	..	48	48	..	..	..	
6	57	42	49	34	49	30	..	..	
9	57	..	52	36	47	37	..	28	
10	..	41	..	24	..	..	..	..	
11	53	..	53	47	50	38	..	..	
12	52	41	47	37	43	33	40	32	
13	47	22	..	..	36	25	..	..	
14	57	41	48	41	48	33	48	37	
17	58	42	52	42	47	38	47	..	
18		40		33	41	31	..	..	
19	54	..	57	47	50	..	..	..	
21	48	42	40	37	38	32	39	35	
22	50	39	50	43	45	30	43	..	
23	58	..	50	37	..	..	47	..	

the reaction of normal persons as a group. Table 3 gives the average values and the lowest values of the 23 patients. The values of 4 patients with coronary occlusion are indicated as a separate group (patients 9, 17, 21 and 22).

The average values and the lowest values of the patients are considerably lower than those of the normal subjects (table 1).

The analysis of table 2 shows that the values of the patients shift into different categories for the different maximum and minimum values. Thus, for instance, for patient 17 all values but one are in the group "pathologic decrease"; the minimum value for the second performance of the left hand is in the group "probable decrease." Especially pronounced is the shifting of the values of patient 10; the initial value for the right hand is high, 70, and in the category "decrease not probable." During the first performance it falls to the minimum value of 41. Although the

TABLE 3.—*Average and Lowest Values of Motor Impulse Frequency in Patients*

	Right Hand				Left Hand			
	First Performance		Second Performance		First Performance		Second Performance	
Values	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum
Averages of values of all patients (23)	60.1	45.4	56.5*	44.5*	52.5	46.4	53.8*	42.8*
Lowest values.....	43	22	40	24	36	25	30	28
Averages of values of patients with coronary occlusion (4)	53.2	42.0	48.5	39.5	44.3	34.3	44.8	35.5

* The values of only 22 patients were used in calculating this average.

initial frequency seems to be normal in this case, the difference between maximum and minimum values is enormously increased, suggestive of a pathologically increased fatigability of the motor centers.

A pathologic deviation must be assumed even if one of the values of a patient (of a total of eight maximum and minimum values) is below the normal lowest limit (L). The more of the values lie in the category "pathologic decrease" and the lower the values, the more pronounced is the pathologic deviation.

We analyzed the number of maximum and minimum values which are in the category "pathologic decrease" for the different patients. As the total of maximum and minimum values amounts to eight, the highest possible number of pathologically decreased values is eight. The minimum possible number of decreased values is, of course, none. In this case all values would be higher than the lowest normal limit (L).

A similar analysis was performed with regard to the combined groups "pathologic decrease" and "probable decrease." The results are

given in table 4. In the first horizontal column the number of maximum and minimum values is indicated, beginning with zero. The second horizontal column concerns the number of patients that corresponds to the number of pathologically decreased values in the first column. The third horizontal column gives the number of patients with values in both categories, "pathologic decrease" and "probable decrease."

For 4 of our patients all eight maximum and minimum values were below the lowest limit. We included patient 13 in this category; he felt too tired to repeat his performance, so that we have obtained only the four values of the first performance. These were the lowest of all values.

For 10 of our patients five of the eight maximum and minimum values are in the zone "pathological decrease," and for 15 patients two values lie in this category. For 8 of the 23 patients all values exceed the lowest limit.

For 10 patients all eight values are lower than the M line, i. e., at least probably decreased. For 12 patients, seven of the eight values are

TABLE 4.—*Number of Patients (Twenty-Three) with Decrease in Eight or Less Maximum and Minimum Values*

Group	8	7	6	5	4	3	2	1	0
Pathologic decrease (below lowest limit of normal)	4	6	8	10	13	14	15	15	8
Pathologic decrease and probable decrease (below mean value)	10	12	15	15	16	18	20	21	2

at least probably decreased, and for 2 patients of 23 all values are above the M line. This analysis shows that the functional state of the motor centers is pathologically decreased in about two thirds of all patients and probably decreased in about nine tenths of all patients. It may be mentioned that some of our patients had no symptoms of decompensation; for instance, patient 1 had fully compensated mitral stenosis.

In order to determine whether the results run parallel with the clinical findings and the actual state of the patients, we have taken for each of the eight maximum and minimum values the five highest and five lowest of our material. A complete correlation cannot be expected, since the deviation of central nervous functions may be different in different patients with similar clinical findings.

What we expect is a higher percentage of compensation in patients in the class with the highest values and a higher percentage of decompensation in patients in the class with the lowest values.

If the fifth value was equal for several patients, all of them were taken. Into this class of those with the five highest values fall 11 patients (1, 2, 4, 5, 7, 8, 10, 11, 15, 16 and 20). With the exception of patients 15, 7 and 4 all of them were without, or with only slight symptoms of,

decompensation. One value of patient 4, who had symptoms of decompensation, falls into the group "decrease possible." But three values of the same patient are in the group "pathologic decrease."

The highest initial values for the right hand are found for patient 20 (78), patient 1 (75) and patients 7 and 10 (70). This frequency drops to 55 for patients 1 and 20 and to 41 for patient 10. In all of these patients the fatigability of motor centers seems to be increased.

In the same way, we analyzed which patients belong to the class with the five lowest values in the eight maximum and minimum values. We found patients 3, 4, 6, 9, 10, 11, 12, 13, 14, 17, 18, 19, 21, 22 and 23 were in this class. Of these 15 patients, 9 had symptoms of decompensation. In 4 of the remaining 6, some additional factors may be responsible for the decrease of motor frequency, for instance, in patients 8 and 6 pain in the arms and chest and in patient 11 renal insufficiency. The low value of patient 10 seems to be partially of nervous origin.

Taken all in all, most of the patients whose values are found to be among the five lowest showed symptoms of decompensation, whereas most patients in the class with the five highest values did not. Hence, there seems to be a parallelism between the frequency of motor impulses and the state of the patient.

The 4 patients with coronary occlusion are among those with the five lowest values. For these patients, six maximum and minimum values are below the lowest limit, and two are below the M line (patient 9); patients 17 and 22 have seven values in the category "pathologic decrease" and one in the category "probable decrease"; all the values of patient 21 lie in the category "pathologic decrease." Thus the results are uniform and consistent in these instances of coronary occlusion. The averages of the values of the patients with coronary occlusion are much lower than those of the other patients (table 3).

The drop of the motor frequency during the test was found to be dependent on the absolute initial value in the normal subjects; the higher the maximum, the more pronounced was the decrease.

We found a positive correlation between the drop of frequency and the maximum value for patients, especially with regard to group correlation, by dividing our material in five series of 4 patients and a sixth series of 3 patients. This separation is justified, because the daily variations may amount to ± 2 impulses. A classification into groups reduces the effect of daily variations to a certain extent. The correlation coefficients, calculated according to Spearman's formula, ranged between 0.97 and 0.99 for both hands and both performances. These high coefficients indicate a close relation between intial value and the drop of frequency. In figure 1 the increase of the drop of frequency (ordinate) with the increase of the maximum frequency (abscissa) is plotted for the first performance, right hand, in a broken line for the normal sub-

jects and in a full line for the patients (mean values of six groups). Both lines run parallel, but that of the patients is considerably higher. This is clear evidence that the fatigability of the motor centers in the patients is appreciably greater than it is in the normal subjects.

In normal subjects, the maximum frequency was almost always identical with the initial value. In 3 subjects (7.1 per cent) of a total of 42 the maximum frequency was reached after the first ten seconds.

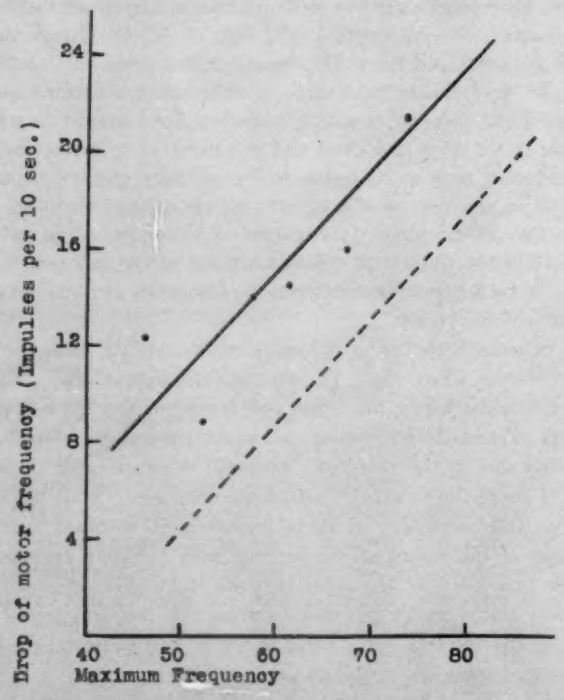

Fig. 1.—Drop in the frequency of motor impulses dependent on the maximum frequency of impulses. The broken line indicates the values for a group of 42 normal subjects, and the unbroken one signifies the values for a group of 23 patients with hypertension or heart disease.

Since in each experiment four performances were tested, a dissociation between the initial value and the maximum frequency was observed in only 3 (1.78 per cent) of 168 test performances of normal subjects. In the patients, the maximum frequency was reached after the first ten seconds in 10 of 23 patients (3, 4, 6, 8, 9, 11, 14, 18, 21 and 22), that is, almost half (43.5 per cent) the total number of patients, or in

15 (16.17 per cent) of a total of 90 performances. Nine of these 10 patients belong to the class with the five lowest values.

The dissociation of initial and maximum frequency which is rare in normal subjects is much more frequently observed in patients. If one takes only patients with symptoms of decompensation, the proportion increases still more; most of these patients reach, in one of the performances at least, the maximum frequency after the first ten seconds, usually between the tenth and the thirtieth seconds. The shape of the

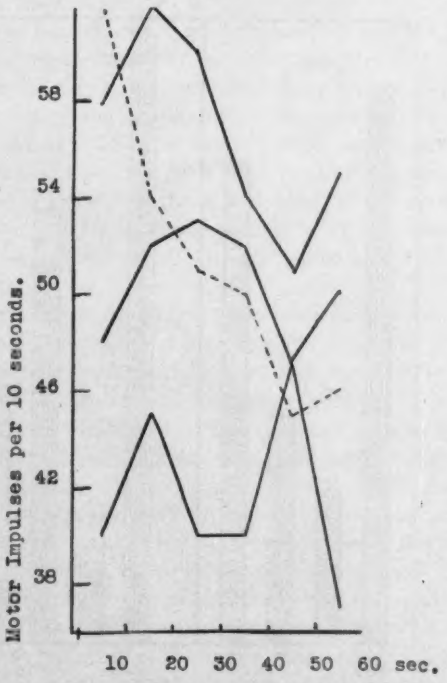

Fig. 2.—Drop in the frequency of motor impulses during a sixty second performance. The broken line indicates the values for a normal subject, and the unbroken lines signify the values for 3 patients with hypertension or heart disease.

curves is greatly altered. Figure 2 shows curves of 3 patients (solid line) compared with a typical normal curve (broken line); the frequency is plotted on the ordinate and the time on the abscissa.

The increase of the impulse frequency during the first ten to thirty seconds is undoubtedly due to adaptation processes. We must assume that the motor centers (and perhaps other centers too) are in a low functional state in these patients during rest. The centers are apt to

develop only a low frequency of impulses. This low excitatory state improves during the performance. The improvement cannot be due to improvement of circulation, ten to thirty seconds being much too short a time for circulatory processes to be effective. The adaptation processes leading to the improvement of the functional state of motor centers must be of nervous origin. Thus, adaptation is not lost in these patients, and even may be enhanced by the low initial functional state. Further observation will reveal whether this is a favorable sign or not.

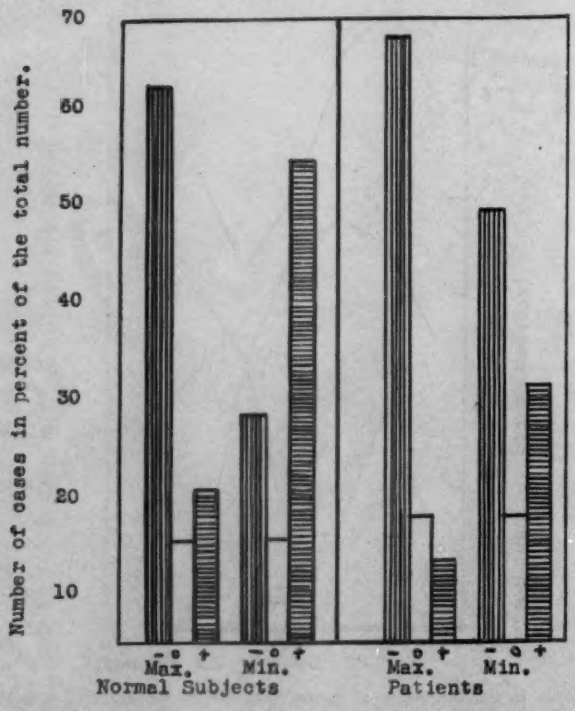

Fig. 3.—The number (in percentage) of normal subjects and patients with hypertension or heart disease with increase (+) or decrease (—) of maximum and minimum values of frequency of motor impulses in the second performance compared with the values of the first performance.

The comparison of the first and the second performance does not give a quantitative expression of fatigue or of adaptation, but it does show whether fatigue or adaptation prevails during the second performance as a result of the antecedent performance. The comparison of the values of the first and of the second performance in the normal subjects revealed an influence of both fatigue and adaptation: As a

result of fatigue, the maximum frequency was lower in the second performance, but, as a result of adaptation, the frequency did not drop as much as in the first performance, so that the minimum value was higher and the second performance as a whole was better stabilized. In order to compare the values of normal subjects and of patients by the same scale, we calculated all values in percentage. Figure 3 shows the result for the right hand. The columns indicate the number of patients in percentage of the total number of subjects. The number of persons with equal values in the first and the second performance is constant for the maximum and minimum values and is 15.8 per cent for the normal subjects and 18.2 per cent for the patients. In the maximum values of the normal subjects the number of instances of negative differences (lower in the second performance) is three times the number of positive differences (higher in the second performance); but in the minimum values the number of positive differences is about twice the number of negative differences. Thus, in the normal subjects the differences shifted from minus to plus when the maximum and minimum values were compared. In the patients, this shift did not occur.

In the patients, the number of negative differences of the maximum values is five times the number of positive differences. In the minimum values, the number of negative differences still exceeds the number of positive differences about one and five-tenths times.

The comparison of the values of the left hand between normal subjects and patients reveals a tendency similar to those of the right hand, although not so distinct. This variation is due to the fact that the maximum values of the left hand are more decreased in patients than in normal subjects, so that the drop of frequency during the performance —as dependent on the absolute value of the maximum frequency— becomes less. The comparison of values for the first and the second performance reveals a much greater prevailing fatigue in patients as an after-effect of the first performance than could be observed in normal subjects. The shape of the curves has revealed the existence of adaptation processes in patients (fig. 2) but their importance is reduced by the overwhelming influence of fatigue.

COMMENT

The maximum frequency of motor impulses is generally decreased in circulatory insufficiency. This result is similar to the decrease of the fusion frequency of flicker as described in a previous paper by an associate and us.[1] The results of these investigations broaden the base of our opinion that circulatory insufficiency leads to a deterioration of central nervous functions, which change seems to be important for the

increased fatigability of patients not only during physical but during mental work and even during rest.

The difference between the normal values and those of patients for maximum frequency of motor impulses is not so distinct as it is for the fusion frequency of flicker. Nevertheless, in 15 of 23 patients at least one maximum or minimum of a possible total of eight values was lower than the lowest normal value. This shows that the four performances the subject has to carry out reveal more deviations than only the measurement of the initial value would do.

The more distinct differences between normal subjects and patients in the fusion frequency of flicker confirm our expectations (see introductory paragraphs). The correlation coefficients between the fusion frequency of flicker and the maximum frequency of the first performances of both hands were calculated. Only the patients with normal vision were taken for this calculation. We found no correlation. It

TABLE 5.—*Influence of the Patient's Condition on the Motor Impulse Frequency*

		Right Hand				Left Hand			
		First Performance		Second Performance		First Performance		Second Performance	
Patient No.	Examination	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum
	1	67	49	62	52	61	47	61	47
2	2	65	48	57	45	58	46	55	41
	1	48	42	40	37	38	32	39	35
21	2	43	31	35	28	30	21	32	23

may be mentioned that in normal subjects there is no correlation between the fusion frequency and the frequency of motor impulses. It is interesting that such a general influence as circulatory insufficiency affects sensory and motor centers differently. Therefore, the combined application of both methods seems to be advisable.

We mentioned that as a rule the frequency of motor impulses does conform with the state of the patients. This generalization is based on results obtained by comparison of different patients. This conclusion could be confirmed by repeated investigations of the patient under different conditions. We had the opportunity to do so in 2 patients (2 and 21). The first was a patient with compensated mitral stenosis complicated by pregnancy. The first examination was performed in the fourth month of pregnancy and the second in the seventh month. All data were lower in the second examination, especially the values in the second performance, which change indicated an increased fatigability (table 5).

Patient 21 came into the hospital a week after the first examination in a much worse condition. He had suffered from severe pains during

the whole night. The values of the second examination were much lower than those of the first (table 5).

The principal reason for the decrease of the frequency of motor impulses in hypertension or heart disease must be the lack of oxygen supply to the central nervous system. The literature on this question, so far as the more general problems are concerned, has been discussed in a preceding paper.[1] Many investigations have been performed with muscular exercise at low oxygen tension, and all authors agree that the working capacity is decreased in these conditions. In most of these investigations types of work have been used in which peripheral physiologic functions are involved, so they do not indicate necessarily a decreased function of the motor centers. Much more significant for our problem is the disturbance of the finer coordinating abilities, for instance, disturbance of handwriting. The process of writing is soon influenced by reduced oxygen tension, and if the oxygen deficiency increases it is rapidly impaired.[7] In the handwriting test, just as in our method peripheral functions do not play any considerable role. But the handwriting test, as a coordination test, concerns the association of different centers.

Although the principal reason for the deterioration of the motor centers is the lack of oxygen in them, we held it possible that pain may play a contributing role. The values of our 4 patients with coronary occlusion are consistently in the group "pathologic decrease," and so are those of patients 3 and 6, with hypertension and pain in the chest.

It seems possible that afferent pain impulses (the origin of the pain seems to be a symptom of deficient oxygen supply in the muscles, according to Katz and associates [8]) spread through the central nervous system and affect the motor centers. The experiments of Forbes and Morrison [9] are strong evidence for this possibility. They observed in anesthetized cats a primary and, after a latent period of one second, a secondary discharge after electric stimulation of the sciatic nerve by induction shocks. Whereas the primary discharge is localized, the secondary discharge is widespread in the cerebral center. Thus, the secondary discharge would reach the motor centers and might, as a subliminal stimulation, alter their state without provoking a direct motor action. There are numerous examples in the physiologic behavior of

7. Jokl, E.: Some Modern Problems of Aviation Medicine, read at the Thirty-Second Annual Meeting of the South African Medical Congress, September 1938.

8. Katz, L. N.; Lindner, E., and Landt, H.: On the Nature of the Substance Producing Pain in Contracting Skeletal Muscle: Its Bearing on the Problems of Angina Pectoris and Intermittent Claudication, J. Clin. Investigation **14**:807, 1935.

9. Forbes, A., and Morrison, B. R.: Cortical Response to Sensory Stimulation Under Deep Barbiturate Narcosis, J. Neurophysiol. **2**:112, 1939.

the central nervous system of the effect of subliminal stimulation. In connection with this Michailov's [10] results are important in that he obtained an increase of the motor chronaxia after different pain stimuli. Possibly these results are the bridge between our findings and the results of the experiments of Forbes and Morrison. For the present, however, we do not regard the additional influence of pain as an established fact.

The results of this and of the previous paper show that disturbance of central nervous processes may be as early a symptom of circulatory insufficiency as the hitherto preferably studied symptom of peripheral decompensation.

SUMMARY

1. The maximum frequency of motor impulses is reduced in circulatory insufficiency.

2. The decrease of the frequency of motor impulses generally conforms to the gravity of the symptoms of decompensation.

3. The fatigability of motor centers in patients with hypertension or heart disease is increased.

4. The shape of frequency fatigue curves is often altered in patients with such a condition.

5. Although there is evidence that adaptation processes are not abolished in such patients, fatigue detectable in the subsequent performance prevails in them as an after-effect of the precedent test, whereas in normal subjects the influence of adaptation diminishes the fatigue in the subsequent performance.

6. The principal reason for the deterioration of motor centers is assumed to be the lack of oxygen in the central nervous system.

10. Michailov, V. D.: Les déformations de la chronaxie et de la rhéobose du muscle strié sous l'influence des différentes irritations douloureuses, Bull. biol. et méd. expér. URSS **6**:504, 1938.

ACACIA IN TREATMENT OF THE NEPHROTIC SYNDROME

WITH SPECIAL REFERENCE TO EXCRETION OF CHLORIDE AND WATER; A REPORT OF CASES

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Elsewhere [1] two of us (A. G. and M. W. B.) have summarized our clinical experience with acacia in the treatment of nephrotic edema. In a consecutive series of 40 patients it was found that 36, or 90 per cent, could be relieved of edema when they followed a regimen of diet, ingestion of potassium nitrate and injections of acacia.

The reason acacia originally was administered is obvious. It was thought that injections of solutions of this colloid material would increase the colloid osmotic pressure of the serum in cases of nephrotic edema and thus facilitate the reabsorption of the fluid resulting from edema. However, actual determination of colloid osmotic pressure before and after a therapeutic course of injections of acacia did not reveal consistent differences. Goudsmit, Binger and Power [2] found that after completion of a course of injections of acacia the colloid osmotic pressure in 43 per cent of a series of 28 patients was definitely increased. In the remaining 57 per cent it was unchanged or decreased, a definite decrease being observed in 18 per cent. There seemed to be little correlation between diuretic response and changes in colloid osmotic pressure. In 4 cases in which definite decreases of colloid osmotic pressure were observed, the therapeutic response was as satisfactory as in 9 cases in which the colloid osmotic pressure increased subsequent to the administration of acacia.

In cases of the nephrotic syndrome the most outstanding deficiency of renal excretion relates to the inability of the patient to eliminate all

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* At the time this work was done Dr. Goudsmit was a Fellow in Medicine of the Mayo Foundation.

1. Goudsmit, A., Jr., and Binger, M. W.: Acacia in the Treatment of the Nephrotic Syndrome, Arch. Int. Med. **66**:1252-1281 (Dec.) 1940.

2. Goudsmit, A., Jr.; Binger, M. W., and Power, M. H.: Unpublished data.

sodium chloride and water ingested during twenty-four hours. The retention and subsequent accumulation of these substances in the lymph and tissue spaces are responsible for the appearance of edema, without which the nephrotic syndrome is usually clinically asymptomatic. In view of the absence of correlation between changes in colloid osmotic pressure and therapeutic effect of injections of acacia, the possibility of acacia's facilitating the excretion of chloride by the kidney thus had to be considered. Experiments on healthy dogs undertaken by Goudsmit, Power and Bollman [3] to investigate this problem showed that the excretion of chloride subsequent to an injection of acacia increased between 4 and 352 per cent, with an average of 189 per cent. This increase was independent of changes in urinary volume and appeared all the more significant because usually, as a consequence of dilution with solution of acacia, the concentration of chloride in the plasma was diminished. The clearances of creatinine and of urea were essentially unchanged.

In view of these results obtained in experiments on dogs, it was decided to extend the study to the investigation of excretion of chlorides by patients who had the nephrotic syndrome. The present study incorporates data on 5 such patients, 4 treated with acacia and 1 treated by means of diet and potassium nitrate, without the use of acacia.

METHODS

Diagnostic criteria, as well as the general regimen of treatment with diet, potassium nitrate and acacia, have been more fully discussed elsewhere.[1] All patients were hospitalized and received a standard low salt (so-called salt-free), high protein diet. Intake of fluids by mouth was restricted and carefully checked. The patients were weighed every morning before breakfast. Urine was collected over twenty-four hour periods starting at 7 a. m. one day and ending at 7 a. m. the next day. For convenience, in the charts presented herein such twenty-four hour periods have been designated as days.

As is well known, diets termed salt free contain small amounts of sodium chloride. Repeated analyses of salt-free, high protein diets served in the hospitals of our city in amounts containing approximately 2,000 calories per twenty-four hours have shown contents of sodium chloride varying between 1 and 2 Gm. Since this amount of sodium chloride is similar to that excreted in feces and perspiration over a period of twenty-four hours, for experiments of relatively short duration, such as are presented herein, the amount of chloride excreted in the urine may be considered to be the net loss of chloride. The additive net loss of chloride from period to period thus represents cumulative chloride loss.

The acacia used in this study was a 6 per cent solution in distilled water, prepared for us by a commercial laboratory.

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3. Goudsmit, A., Jr.; Power, M. H., and Bollman, J. L.: Some Effects of the Injection of Acacia with Special Reference to Renal Function, Proc. Soc. Exper. Biol. & Med. **47**:254-257 (June) 1941.

Urinalysis, determinations of blood urea according to Van Slyke and Cullen, of chloride in the urine according to Wilson and Ball, of plasma chloride according to Osterberg and Schmidt, of carbon dioxide-combining power according to Hawk and Bergheim and of blood urea clearance, concentration of cholesterol in the blood, concentration of the serum proteins and the albumin-globulin ratio were carried out according to the directions of Todd and Sanford.[4] The colloid osmotic pressure of the serum was determined according to the method of Butt, Power and Keys,[5] reported in an article that also contains a description of Power's method for determination of concentration of acacia in serum, which was employed in the present study.

In the charts contained here, the excretion of 5 Gm. of sodium chloride, calculated from the equivalent excretion of chloride, has been represented by a block as high as one representing 1,000 cc. of urine. A loss in weight of 1 Kg. and a cumulative loss of sodium chloride amounting to 5 Gm. have been plotted on an equal scale.

REPORT OF CASES

Case 1.—A 29 year old woman having chronic glomerulonephritis with marked nephrotic features was first admitted to the hospital in 1937, at which time acacia was used successfully.[6] She returned to her home and remained free of edema. Thirteen months after her dismissal from the hospital, when she came back for reexamination, no edema was noted. Albuminuria, graded 4, persisted, but her condition otherwise appeared satisfactory. The patient was directed to continue her regular regimen.

Shortly afterward, because of a change in circumstances, this patient had to start to work to earn her living. From that time on swelling reappeared and increased gradually during the following four months.

On the patient's readmission to the hospital, moderate edema of the feet, legs and lumbosacral region was found. The blood pressure was normal, as were the ocular fundi. Urinalysis showed a specific gravity of 1.032, albumin graded 3, casts graded 1, and occasional erythrocytes. The blood per hundred cubic centimeters contained 26 mg. of urea, 641 mg. of cholesterol and 633 mg. of chloride (expressed as sodium chloride). The carbon dioxide-combining power was 48.5 volumes per cent. The serum per hundred cubic centimeters contained 47 mg. of acacia and 3.8 Gm. of protein. The albumin-globulin ratio was 1:1.1. The clearance of urea amounted to 20.1 cc. per minute at a volume of 10 cc. per hour.

This patient's course in the hospital is illustrated in figure 1. As can be seen, before special therapy was instituted the urinary volume amounted to 350 to 400 cc. each twenty-four hours; the excretion of chloride was 1.1 Gm. On the third day, 500 cc. of a 6 per cent solution of acacia was administered in the morning and 500 cc. early in the evening. The urinary volume that day rose to 2,800 cc. and the excretion of sodium chloride to 17.2 Gm. During the next four days

4. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods: A Working Manual of Clinical Pathology, ed. 9, Philadelphia, W. B. Saunders Company, 1939.

5. Butt, H. R.; Power, M. H., and Keys, A.: The Concentration of Acacia in the Serum, Its Rate of Excretion, and Its Effect on the Colloid Osmotic Pressure Following Intravenous Injection in Cases of Cirrhosis of the Liver, J. Lab. & Clin. Med. **24**:690-695 (April) 1939.

6. The course of this patient's disease in 1937 has been reported by Goudsmit and Binger (case 1).[1]

the excretion of sodium chloride continued to be considerably above the control value, and after one more injection of 500 cc. of a 6 per cent solution of acacia the patient had lost a total of 48 Gm. of sodium chloride and 3.2 Kg. (7 pounds) of weight. At that time, to reenforce the effect of acacia, administration of potassium nitrate orally was started. This procedure led to additional loss of weight, as well as of chloride. The intravenous administration of 1 cc. of esidrone (the sodium salt of pyridinedicarboxy-β-mercuri-ω-hydroxypropylamide-theophylline) was followed by only a slight increase in excretion of sodium chloride and of water, and on the fourteenth day the patient was dismissed from the hospital, having lost 74 Gm. of sodium chloride and 4.7 Kg. (10.3 pounds) of weight, with, as noted by the physician, "perhaps just a trace of lumbar edema." Three days after dismissal, the patient's serum proteins were 2.8 Gm. per hundred cubic centimeters, the albumin-globulin ratio was 1.1 : 1 and the concentration of acacia in the serum was 1,950 mg. per hundred cubic centimeters. One day before

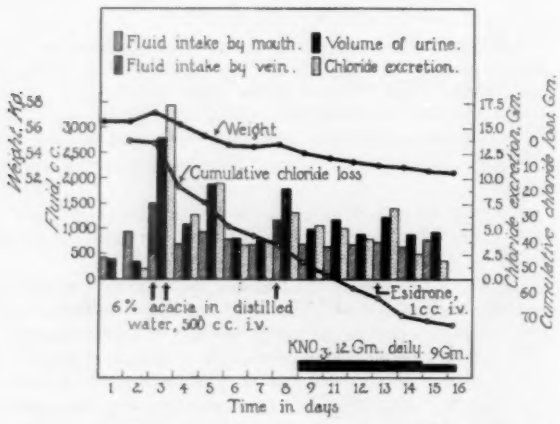

Fig. 1.—Excretion of water and of chlorides by a patient (case 1) who had nephrotic edema, treated with intravenous injections of acacia and with potassium nitrate given by mouth. Daily diet: protein, 75 Gm.; calories, 1,800; salt, none; fluids by mouth, 800 cc. Esidrone is the sodium salt of pyridinedicarboxy-β-mercuri-ω-hydroxypropylamide-theophylline.

dismissal the blood plasma per hundred cubic centimeters contained 521 mg. of cholesterol and 575 mg. of chloride (expressed as sodium chloride) per hundred cubic centimeters.

In view of the occurrences attendant on this case, it is obvious that the administration of acacia was followed by a most striking increase in the excretion of water and of sodium chloride. On a number of occasions after the administration of acacia, the concentration of sodium chloride in the twenty-four hour specimen of urine was more than 0.5 per cent. After the administration of esidrone, the increase in excretion of water and of sodium chloride remained considerably below the amounts excreted after the administration of acacia alone.

CASE 2.—A 19 year old unmarried woman was admitted to the clinic on Nov. 28, 1938. She stated that she had been suffering from swelling around the eyes for the previous three years. A year and a half previously her ankles had begun to be slightly swollen, and a year previously, although she had remissions, her condition gradually had become worse.

On examination the patient's face was found to be slightly puffy. Considerable edema of the sacral and the lumbar regions and of the legs and ankles was found. She had ascites, graded 2, and fluid in the left side of the thorax could be demonstrated on physical examination; the latter observation was confirmed by roentgenologic examination. The blood pressure was normal, and results of examination of the ocular fundi were essentially irrelevant. Urinalysis revealed a specific gravity of 1.027, albumin graded 4, casts graded 3, an occasional erythrocyte and pus graded 2. The blood per hundred cubic centimeters contained 42 mg.

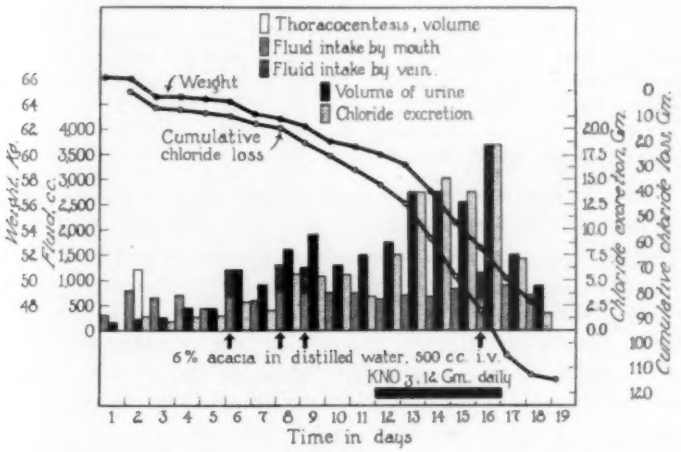

Fig. 2.—Excretion of water and of chlorides by a patient (case 2) who had nephrotic edema, treated with intravenous injections of acacia and with potassium nitrate given by mouth. Daily diet: protein, 80 Gm.; calories, 1,800; salt, none; fluids by mouth, 800 cc.

of urea and 641 mg. of cholesterol. The concentration of serum proteins was 2.8 Gm. per hundred cubic centimeters, and the albumin-globulin ratio was 2.1 : 1. A diagnosis of chronic glomerulonephritis with marked nephrotic features was made.

The patient's course in the hospital is illustrated in figure 2. On the second day thoracentesis was performed, and 1,000 cc. of clear fluid was removed. The protein content of this fluid was 0.2 per cent, and the specific gravity was 1.011. The concomitant loss of sodium chloride, for the purposes of charting, was estimated at 5 Gm. The volume of urine for twenty-four hours varied between 150 and 450 cc., and excretion of sodium chloride for a similar period, between 0.8 and 1.5 Gm. On the day of the first injection of acacia a considerable increase in urinary volume, as well as in excretion of chloride, was seen, and after two

more injections the urinary volume increased to 1,900 cc. and the excretion of chloride to 5.3 Gm. per twenty-four hours. Thus, by the morning of the twelfth day this patient had lost a total of 37 Gm. of sodium chloride and 6.1 Kg. (13.4 pounds) of weight, of which the loss of 5 Gm. and of 1 Kg. respectively was caused by the mechanical removal of the fluid from the thorax. At this time the concentration of acacia was 1,800 mg. per hundred cubic centimeters of serum.

As a consequence of the administration of potassium nitrate, the urinary volume, as well as the excretion of chloride in the urine, was increased considerably. For a period of three days the excretion of water and of sodium chloride was essentially unchanged. When one more injection of acacia was administered, on the sixteenth day, the urinary volume increased to 3,700 cc. per twenty-four hours, which is nearly 1,000 cc. more than the volume during treatment with potassium nitrate alone. The amount of chloride excreted was 18.3 Gm., which is also in excess of that excreted on any one of the three previous days. As a consequence of these procedures, the patient rapidly lost weight, and on December 16 it was noted that there remained "just a trace of edema below the left elbow, no actual clinical edema elsewhere." One day after the last injection of acacia its concentration in the serum was 1,990 mg. per hundred cubic centimeters.

During her stay in the hospital, the patient lost a total of 16.8 Kg. (37.0 pounds) of weight and 114 Gm. of sodium chloride.

It would seem that in this case the concentration of sodium chloride in the twenty-four hour specimen of urine was essentially unchanged by the administration of acacia or potassium nitrate or the combination of the two. However, the absolute quantities excreted per twenty-four hours were considerably increased after the treatment was instituted. It is noteworthy that the first injection of acacia was not successful in producing a prolonged increase in the excretion of chloride and of water. However, after the second and third injections the increased excretion of chloride and of water appeared well maintained.

Case 3.—The history of this patient has been reported elsewhere[1] (case 5). It might be summarized as follows: On a previous occasion a diagnosis of chronic glomerulonephritis with nephrotic features had been made, and the patient had been treated in the hospital with restriction of diet, potassium nitrate and injections of acacia. He had been dismissed free of edema and had been advised to continue the diet and the oral ingestion of potassium nitrate. He had remained free of edema until, after a gastrointestinal upset, he had discontinued ingestion of the potassium nitrate. After this, the swelling had recurred.

On the patient's readmission, urinalysis showed a specific gravity of 1.025, albumin graded 3, casts graded 3, occasional erythrocytes and pus graded 1. The blood per hundred cubic centimeters contained 22 mg. of urea, 490 mg. of cholesterol, 633 mg. of chloride (expressed as sodium chloride) and 3.1 Gm. of serum proteins. The carbon dioxide–combining power was 57 volumes per cent. The albumin-globulin ratio was 1.1 : 1, and the serum contained 225 mg. of acacia per hundred cubic centimeters. The colloid osmotic pressure of the serum was 95 mm. of water. The patient's course in the hospital is illustrated in figure 3. The response to injections of acacia, an increase in the concentration of this substance

in the serum after the third injection to 1,770 mg. per hundred cubic centimeters, was striking. The urinary volume increased to 2,500 cc. per twenty-four hours, and the excretion of sodium chloride in one day was as high as 14.1 Gm. The patient lost weight rapidly, so that on the day that the administration of potassium chloride was started his weight was 1 Kg. (about 2 pounds) more than it had been at the time of his previous dismissal from the hospital, when he was adjudged to be free of edema. He had lost 55 Gm. of sodium chloride and 6 Kg. (about 14 pounds) of weight. Despite the administration of potassium chloride, the chloride balance continued to be definitely negative. After a fourth injection of acacia in distilled water (which increased its concentration in the serum to 2,015 mg. per hundred cubic centimeters), 9.3 Gm. more of sodium chloride was lost. At the time of dismissal from the hospital, this patient's loss of weight amounted to 7 Kg. (approximately 15.4 pounds) and the loss of sodium chloride to 77 Gm.

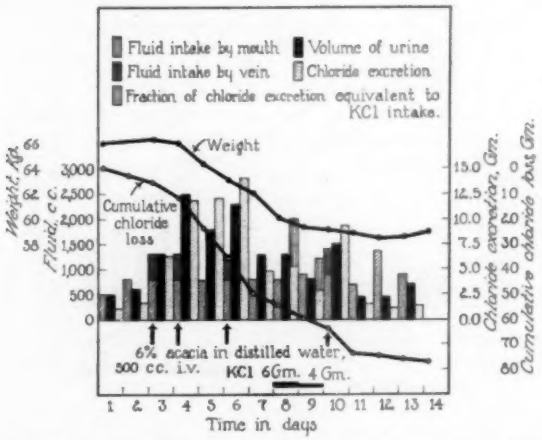

Fig. 3.—Excretion of water and of chlorides by a patient (case 3) who had nephrotic edema, treated with intravenous injections of acacia and with potassium chloride given by mouth. In the calculation of the "cumulative chloride loss" the equivalent in sodium chloride of the potassium chloride administered is considered as extra intake. Daily diet: protein, 80 Gm. (from the ninth day on: protein, 100 Gm.); calories, 2,000; salt, none; fluids by mouth, 800 cc.

In the report just presented it can be observed that the response of the excretion of water and of chloride following the injection of acacia was again definite. The concentration of chloride in the urine, which on the first two days of hospitalization was approximately 0.25 per cent, on many occasions increased to considerably more than 0.5 per cent subsequent to the administration of acacia. Potassium chloride, which was administered for only two days, with a total dose of 10 Gm., did not appreciably influence the course of the patient in the hospital. It is

obvious that after its administration a concentration of chloride in the urine, expressed as sodium chloride, was reached which was definitely more than the concentrations observed under other circumstances.

Case 4.—A 69 year old man stated that four weeks previous to admission to the hospital he had noticed swelling of his abdomen, followed by swelling of his feet and legs and later of his face and hands. On this patient's admission, edema of the abdominal wall, graded 1 to 2, was found, as well as ascites, graded 1 to 2, and edema of the lumbosacral region and the legs and ankles, graded 2. The systolic blood pressure was 170 and the diastolic pressure was 90, expressed in millimeters of mercury; peripheral sclerosis, graded 2, was noted. Examination of the ocular fundi revealed the arterioles to be somewhat narrowed, with sclerosis, graded 1, of the chronic hypertensive type. Urinalysis showed a specific gravity

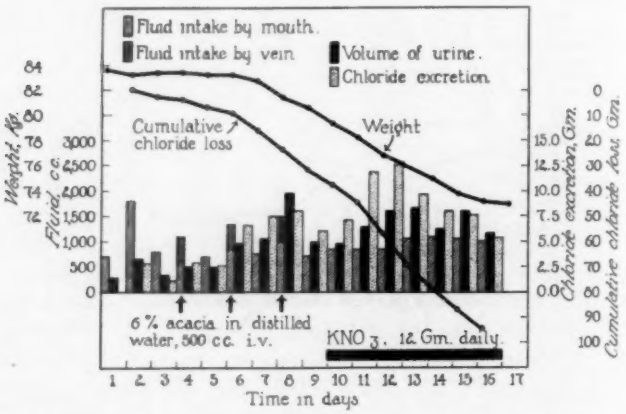

Fig. 4.—Excretion of water and of chlorides by a patient (case 4) who had nephrotic edema, treated with intravenous injections of acacia and with potassium nitrate given by mouth. Daily diet: protein, 70 Gm.; calories, 1,800; salt, none; fluids by mouth, 800 cc.

of 1.033, albumin graded 4, casts graded 3, an occasional erythrocyte and pus graded 1. The blood per hundred cubic centimeters contained 30 mg. of urea, 438 mg. of cholesterol, 561 mg. of chloride (expressed as sodium chloride) and 4.5 Gm. of serum proteins. The carbon dioxide-combining power was 54.1 volumes per cent. The albumin-globulin ratio was 1.2:1, and the clearance of urea was 65.2 cc. per minute, with a volume of 50 cc. per hour. A diagnosis of chronic glomerulonephritis with nephrotic features was made.

Features of the water and the chloride balance during the period of hospitalization are illustrated in figure 4. Three injections of acacia (bringing the concentration of this substance in the serum to 1,380 mg. per hundred cubic centimeters) on alternate days increased excretion of water and of chloride, so that on the morning of the day that administration of potassium nitrate was begun the patient

had lost 32 Gm. of sodium chloride and 4.3 Kg. (9.5 pounds) of weight. A definite diuretic response was obtained after the use of potassium nitrate, but the volume of urine never became as large as it had been on the day of the third injection of acacia. However, the excretion of chloride was considerably augmented. One day before dismissal the patient was entirely free of edema; he had lost 10.4 Kg. (22.9 pounds) of weight and 94 Gm. of sodium chloride. At the time of dismissal from the hospital, the blood per hundred cubic centimeters contained 44 mg. of urea, 309 mg. of cholesterol and 540 mg. of chloride (expressed as sodium chloride). The carbon dioxide–combining power was 61.7 volumes per cent.

Prior to the administration of acacia, the concentration of chloride in a twenty-four hour specimen of urine was approximately 0.5 per cent. After the injections, however, the concentration on nearly every day was maintained above this figure. On one day it was nearly 0.8 per cent. This relative excess in excretion of chloride over excretion of water was still further accentuated by the administration of potassium nitrate. Reenforcement of the diuretic measures with potassium nitrate in this case appeared to increase the rate of loss of chloride slightly more than it affected the rate of loss of weight. The concentration of chloride in the blood at the conclusion of the administration of potassium nitrate was essentially the same as it had been at the beginning.

Case 5.—A 36 year old man was admitted to the clinic on Dec. 17, 1938. He stated that he had noted slight fatigue during the previous two months. One month before admission he had become aware of increased swelling of the feet, legs, arms and face. Erythrocytes and considerable albumin had been found in the urine, and he had gone to bed. Since that time his urinary volume had increased to approximately 2 quarts (1,892 cc.) daily, and he had lost 8 to 10 pounds (3.6 to 4.5 Kg.) of weight. Examination revealed edema, graded 2, of the sacral region, abdominal wall, ankles and legs. Peripheral sclerosis, graded 2, was noted. The systolic blood pressure was 168 and the diastolic pressure 110, expressed in millimeters of mercury. Examination of the ocular fundi revealed nothing abnormal except for a few hemorrhages, which the examining ophthalmologist interpreted as probably associated with anemia rather than with hypertension. Urinalysis showed a specific gravity of 1.015, albumin graded 4, casts graded 3, erythrocytes graded 4 and leukocytes graded 1. The blood per hundred cubic centimeters contained 10.8 Gm. of hemoglobin, 42 mg. of urea, 236 mg. of cholesterol, 614 mg. of chloride (expressed as sodium chloride) and 4.6 Gm. of serum protein. The carbon dioxide–combining power was 63.6 volumes per cent. The albumin-globulin ratio was 1.1:1. A diagnosis of subacute or chronic glomerulonephritis with edema and mild secondary anemia was made.

Without any therapy other than rest in bed and a salt-free, high protein diet, the urinary volume per twenty-four hours soon increased to as much as 2,000 cc. and the daily excretion of sodium chloride amounted to approximately 4 Gm. By the morning of the fifth day (fig. 5) the patient had lost 5.1 Kg. (11.2 pounds) of weight and more than 12 Gm. of sodium chloride. When subsequently potassium nitrate was administered, his improvement continued at an even more rapid rate. The maximal urinary volume was 2,500 cc. per twenty-four hours and the

maximal excretion of chloride was 11.2 Gm. in a similar period. When he was dismissed on the nineteenth day, he was free of edema and had lost 15.3 Kg. (approximately 33.7 pounds) of weight and more than 126 Gm. of sodium chloride. Shortly before dismissal of the patient the blood per hundred cubic centimeters contained 578 mg. of chloride (expressed as sodium chloride) and 6 Gm. of serum proteins. The carbon dioxide–combining power was 60.7 volumes per cent. The albumin-globulin ratio was 1.2:1.

This case differs from the 4 cases previously described in that the patient's condition was considerably less severe. The concentration of serum proteins was higher than in any of the other cases, and the excretion of sodium chloride and of water, with dietary treatment alone, was considerably more than the intake. In view of the ease with which the

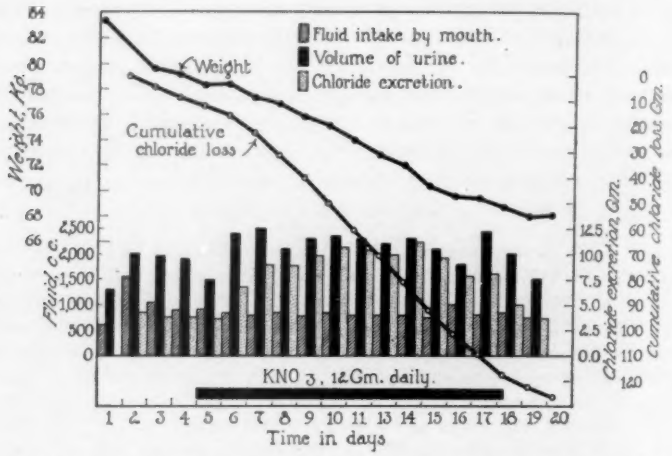

Fig. 5.—Excretion of water and of chlorides by a patient (case 5) who had edema, treated with potassium nitrate administered orally. Daily diet: protein, 80 Gm.; calories, 2,000; salt, none; fluids by mouth, 800 cc.

edema was mobilized, the use of acacia was deemed unnecessary. The response to potassium nitrate was rather typical.

COMMENT

We have previously stated that in the cases of the nephrotic syndrome the major deficiency of renal excretion is in the elimination of sodium chloride and of water. This inability on the part of the kidney appears definitely related to low concentration of serum proteins or to lowered colloid osmotic pressure of the serum. After injection of acacia, judging by the results obtained in the cases presented, the excretion of water and of sodium chloride appears to improve so that considerably more water

and chloride are excreted. Sometimes the concentration of sodium chloride in the twenty-four hour specimen of urine appears to be definitely increased after injection of acacia, and sometimes it does not. Potassium salts in general, the potassium nitrate in particular,[7] cause an increase in the rate of excretion of sodium and of chloride, and of water as well. The combined use of acacia and potassium nitrate seems to allow removal of edema fluid in a large percentage of adult patients who have the nephrotic type of edema.

The mechanism by which acacia increases the excretion of water and of sodium chloride is unexplained at present. As is well known, intravenous injection of acacia causes an increase in the volume of the circulating blood, and, according to Peters'[8] suggestion, "It may well be the fullness of the blood stream which provokes the diuretic response on the part of the kidney." Measurements of the actual increase in the volume of the circulating blood after single injections of acacia, such as were performed by Lepore,[9] show that this increase is of the same order of magnitude as that observed after ingestion of large amounts of water or after intravenous injection of an appreciable volume of a hypertonic solution. Nevertheless, the effects of the latter agents on a patient who has a severe type of nephrotic edema are far from identical with the effects of acacia. In addition, in another condition in which the volume of circulating blood is increased, namely, congestive heart failure, edema is regularly present. Thus, although the increase in the volume of the circulating blood might play an important part in the mobilization of the edema fluid, the mechanism by which this could happen can be described only in general terms. Experimental evidence and quantitative data to substantiate such a descriptive picture are lacking. On the other hand, results of studies on healthy dogs, mentioned earlier, indicated that the excretion of chloride is increased considerably after the administration of acacia.

Renal excretion as interpreted at the present time is effected through glomerular filtration and tubular reabsorption and secretion. In the normal human adult, chloride is supposed to be present in the glomerular filtrate in a concentration essentially similar to its concentration in the plasma. A quantity of approximately 150 cc. is ultrafiltered each minute, and approximately 130 Gm. of sodium chloride passes through the glomerular filter in twenty-four hours. Most of this chloride, of course,

7. Keith, N. M., and Binger, M. W.: Diuretic Action of Potassium Salts, J.A.M.A. **105**:1584-1591 (Nov. 16) 1935.

8. Peters, J. P.: Body Water: The Exchange of Fluids in Man, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

9. Lepore, M. J.: Acacia Therapy in Nephrotic Edema, Ann. Int. Med. **11**: 285-296 (Aug.) 1937.

is reabsorbed by the tubules. In patients with the nephrotic syndrome, no essential disturbance of glomerular function, except increased permeability for protein, is supposed to exist. Thus, the difference between the excretion of chloride by the normal person and the excretion by the patient with nephrotic edema must be the result of increased tubular reabsorption of chloride. It is not clear how this excessive reabsorption from the lumen of the tubule into the blood stream could be explained directly by the decreased colloid osmotic pressure of the serum. Nevertheless, little doubt exists that there is a definite cause and effect relation between decreased colloid osmotic pressure and increased tubular reabsorption, because the tendency toward edema and the retention of water and of salt appears to be common to all conditions of advanced hypoproteinemia. Since injections of acacia do not significantly change the colloid osmotic pressure of the serum of patients who have the nephrotic syndrome and since the injection of this substance, judging by experiments on dogs, does not affect the rate of glomerular filtration, it seems to us that the most plausible explanation for the diuretic action of acacia relates to the reestablishment of a more normal rate of tubular reabsorption of water and of chloride.

SUMMARY

Intravenous injection of acacia into 4 patients who had the nephrotic type of edema was followed by marked increases in urinary excretion of water and of chloride (expressed in terms of the sodium salt). This increased excretion of sodium chloride and of water brings about a reversal of conditions which is significant and beneficial, considering the excretion by untreated patients. Neither increases in the volume of the circulating blood nor changes of colloid osmotic pressure appear to account for this change in renal function. Experiments on animals have also demonstrated this increased excretion of chloride after intravenous administration of acacia. It is suggested that an analogous effect might well be responsible for the diuretic response of these patients.

DIAGNOSIS OF CARCINOMA OF THE PANCREAS

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With progressive advance in surgical technic radical but curative operations have been made possible in cases of carcinoma of the pancreas. For these operations to be successfully employed, however, it is of utmost importance that an early diagnosis be made. Yet accuracy of diagnosis at any stage is not great, especially when there is no jaundice or when the body or tail of the pancreas is predominantly involved (table 1). In many cases the disease is incorrectly diagnosed

TABLE 1.—*Diagnostic Accuracy in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Condition Was Correctly Diagnosed	Percentage
1920	Speed, K.: Am. J. M. Sc. **160**:1, 1920..	52	3	5.7
1922	Eusterman [26]	26 (without jaundice)	8	30.7
		22 (with jaundice)	22	100.0
1935	Ransom [7]	16 (body and tail)	3	18.7
1939	Duff [2c]	16 (body and tail)	0	0.0
		132	36	Average 27.2

and its presence is missed in the early stages because in the mind of the average physician certain impressions of traditional diagnostic criteria have persisted despite the fact that they have been repeatedly shown to be false.

This study was undertaken to establish, first, the current leading impressions of the diagnostic criteria of the disease carcinoma of the pancreas, and second, to determine from a review of a series of proved cases observed by my associates and me at the Graduate Hospital of the University of Pennsylvania, as well as of similar series reported in the literature, what the outstanding manifestations of carcinoma of the pancreas really are.

Read before the College of Physicians of Philadelphia, Oct. 28, 1940.

From the Gastrointestinal Service of Dr. Henry L. Bockus, Department of Medicine, Graduate Hospital of the University of Pennsylvania.

To achieve the first aim, a poll was taken among representative groups of fourth year medical students, interns and residents, graduate students and general practitioners in practice five years or less. The poll included 120 persons from thirty-four medical schools, of which three were leading foreign schools. Each person was given an explanation of the nature of the poll being taken but was not told the disease in question. He was then asked to state that feature which he most closely associated with and felt was most commonly to be found and expected in patients with carcinoma of the pancreas.

Many objections may be raised to such a poll. The replies may be said to indicate merely psychologic associations; yet the fact that one given feature is held to be outstanding and characteristic does not mean that other features are not likewise appreciated. This objection and others that might be made are valid beyond question. It should be understood, however, that the poll was meant to determine only common leading impressions and from these to secure a rough index of the trend of diagnostic thought that is uppermost in the minds of younger physicians. Fixed leading impressions of diagnostic criteria must of necessity influence the path of inquiry which any given person will take. In fact, a number of the physicians questioned stated in the course of conversation after the poll that in the absence of the leading and characteristic feature which they associated with carcinoma of the pancreas they would probably fail to think of the disease at all.

It may be seen from this poll (table 2) that 43 per cent of these younger, and presumably better trained, persons expressed the belief that painless jaundice is the most common and characteristic feature of carcinoma of the pancreas. Another 50 per cent stated that simple jaundice is the predominant characteristic, although many qualified the jaundice as being deep and progressive. Only 2.5 per cent expressed the belief that pain is of outstanding consequence. The vast majority (92.5 per cent), therefore, were convinced that jaundice, usually painless and progressive, is the single feature which is paramount in carcinoma of the pancreas.

The second part of this study is based partly on an analysis of the cases of primary carcinoma of the pancreas seen at the Graduate Hospital of the University of Pennsylvania from March 1927 to April 1940. During this period the diagnosis of primary carcinoma of the pancreas was made in 42 cases, in 35 of which it was proved by laparotomy or necropsy. Since 1 of the 35 proved cases has been previously reported,[1] the analysis was restricted to the remaining 34 cases. In 25 of these the diagnosis was confirmed by laparotomy only with positive

1. Yaskin, J. C.: Nervous Symptoms as Earliest Manifestations of Carcinoma of the Pancreas, J. A. M. A. **96**:1664 (May 16) 1931.

TABLE 2.—*Poll of Impressions of Chief Diagnostic Criterion in Cases of Carcinoma of the Pancreas*

Status	Number Polled	Number of Different Schools Represented	Diagnostic Criteria																	
			Painless Jaundice		Jaundice		Pain		Loss in Weight		Anorexia		Dyspepsia		Enlarged Gallbladder		Deformed Duodenum		Diabetes	
Fourth year medical students.	34	4	10		23		..		..		..		..		1		..		..	
Interns and residents	36	14	24		10		1		..		..		..		..		1		..	
Graduate students	26	23	9		14		1		..		1		1		..		..		..	
General practitioners (in practice 5 years or less)	24	6	9		12		1		1		..		..		..		..		1	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total.....	120	34	52	43.3	59	49.1	3	2.5	1	0.8	1	0.8	1	0.8	1	0.8	1	0.8	1	0.8
				92.5%				2.5%						5.0%						

findings in biopsy sections in 6, both by laparatomy and by necropsy in 5 and by necropsy alone in 4. To this analysis have been added the findings reported by other authors in similar previous studies.

GENERAL FEATURES

Incidence.—Primary carcinoma of the pancreas is by no means a rare disease. Estimates as to the frequency of its occurrence have been variously made.[2] On the basis of these it may be stated that primary carcinoma of the pancreas causes 1 to 2 per cent of all deaths in the population at large, is present in about 0.1 per cent of all patients admitted to large general hospitals, is observed at 0.3 to 0.75 per cent of all autopsies and comprises 1 to 2 per cent of all carcinomas.

Sites and Extent of Anatomic Involvement.—Ever since the classic descriptions by Bard and Pic [3] and by Chauffard [4] it has been customary to consider the symptoms of carcinoma of the pancreas as divided into those of carcinoma of the head and those of carcinoma of the body and tail. It is felt that involvement of each area produces manifestations so characteristic as to form a separate syndrome. By the same token, it is believed that the carcinomatous process will affect predominantly one or the other part of the gland.

In a collected series of 1,449 cases the head of the pancreas was involved in 81.7 per cent (table 3). The frequency of involvement of

2. (*a*) D'Aunoy, R.; Ogden, M. A., and Halpert, B.: Carcinoma of the Pancreas: An Analysis of Forty Autopsies, Am. J. Path. **15**:217, 1939. (*b*) Dublin, L. I.; Kopf, E. W., and Van Buren, G. H.: Cancer Mortality Among Insured Wage Earners and Their Families, New York, Metropolitan Life Insurance Company, 1925, p. 71. (*c*) Duff, G. L.: The Clinical and Pathological Features of Carcinoma of the Body and Tail of the Pancreas, Bull. Johns Hopkins Hosp. **65**:69, 1939. (*d*) Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 746. (*e*) Futcher, T. B.: Cancer of the Pancreas, Tr. A. Am. Physicians **34**:284, 1919. (*f*) Hick, F. K., and Mortimer, H. M.: Carcinoma of the Pancreas, J. Lab. & Clin. Med. **19**:1058, 1934. (*g*) Hoffman, F. L.: Cancer of the Pancreas, New England J. Med. **211**:165, 1934. (*h*) Kiefer, E. D.: Carcinoma of the Pancreas, Arch. Int. Med. **40**:1 (July) 1927. (*i*) Leven, N. L.: Primary Carcinoma of the Pancreas, Am. J. Cancer **18**:852, 1933. (*j*) Marble, A.: Diabetes and Cancer, New England J. Med. **211**:339, 1934. (*k*) McKittrick, L. S., and Root, H. F.: Diabetic Surgery, Philadelphia, Lea & Febiger, 1928. (*l*) Ransom, H. K.: Carcinoma of the Pancreas and Extrahepatic Bile Ducts, Am. J. Surg. **40**:264, 1938. (*m*) Rives, J. D.; Romano, S. A., and Sandifer, F. M., Jr.: Carcinoma of the Pancreas, Surg., Gynec. & Obst. **65**:164, 1937. (*n*) Shapiro, P. F., and Lifvendahl, R. A.: Tumors of the Extra-Hepatic Bile Ducts, Ann. Surg. **94**:61, 1931.

3. Bard, L., and Pic, A.: Cancer primitif du pancréas, Rev. de méd. **8**:257, 1888.

4. Chauffard, M. A.: Le cancer du corps du pancréas, Bull. Acad. de méd., Paris **60**:242, 1908.

the head is less (72.2 per cent) in those cases in which the diagnosis is made from accurate postmortem examinations than in those in which the diagnosis rests solely (93.1 per cent) or to a large extent (79.9 per cent) only on the observations made at the time of operation. Necropsy data indicate that overlapping involvement of various parts of the gland

TABLE 3.—*Incidence of Involvement of Head in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Head Involved	Percentage
	Diagnosis at Operation			
1934	Reinhoff and Lewis [6]	87	81	93.1
	Diagnosis at Operation or Necropsy			
1922	Eusterman [9g]	48	33	68.7
1924	Cameron [9b]	61	45	73.8
1927	Kiefer [9h]	33	28	84.8
1933	Eusterman and Wilbur [9k]	70 (without jaundice)	42	60.0
1934	Marble [9j]	21	21	100.0
1935	Ransom [7]	74	58	78.3
1937	Rives, Romano and Sandifer [9m]	96	82	85.4
1938	Ransom [9i]	83	65	78.0
1939	MacKinnon [9q]	45	42	93.3
1940	Levy and Lichtman [5]	122	103	84.4
1941	Berk	29	26	89.6
		682	545	Average 79.9
	Diagnosis at Necropsy			
1933	Leven [9l]	97	78	80.4
1934	Hick and Mortimer [9f]	49	26	54.0
1939	D'Aunoy, Ogden and Halpert [9a]	40	21	77.5
1939	Duff [9c]	50	31	62.0
1939	Grauer [9k]	34	29	85.2
		270	195	Average 72.2
	Basis of Diagnosis Not Stated			
1928	Ewing [9d]	354	314	88.7
1939	Zollinger and Kevorkian [9r]	56	49	87.5
		410	363	88.5
Entire series		1,449	1,184	Average 81.7

is the rule in the vast majority of cases of carcinoma of the pancreas. Even in carefully selected cases diffuse overlapping is apparent. Among 122 verified cases, Levy and Lichtman [5] could find but 19 in which

5. Levy, H., and Lichtman, S. S.: Clinical Characterization of Primary Carcinoma of the Body and Tail of the Pancreas, Arch. Int. Med. **65**:607 (March) 1940.

they were satisfied that only the body and tail were affected, and yet in some of these there was what they called "terminal" involvement of the head.

It is impossible to estimate accurately the extent of involvement at the operating table. Of 109 patients on whom an operation had been done for carcinoma of the pancreas, Rienhoff and Lewis [6] were unable to establish the site affected in 22. Of our 34 cases, the site of the carcinomatous process in the pancreas was indeterminate in 5. Yet Ransom,[7] in presenting 16 cases illustrative of the syndrome to be expected when carcinoma localizes itself to the body and tail, established the localization in 14 cases by means of the operative observations only.

How much even small areas of involvement in a given part of the gland contribute to the symptom picture cannot be evaluated. As will be shown later, even with certain areas dominantly affected the resultant symptom pictures bear much in common, and this may be due to minute but definite overlapping involvement of various parts of the gland.

It is impossible to distinguish at the time of operation between carcinoma of the common duct and carcinoma of the pancreas. Ransom [21] reported that of 6 patients given an operative diagnosis of carcinoma of the pancreas 3 were proved at necropsy to have carcinoma of the common duct. In 2,500 autopsies Shapiro and Lifvendahl [2n] encountered carcinoma of the extrahepatic bile ducts three times as frequently as carcinoma of the head of the pancreas, and in 30 autopsies Ransom [21] found it one and a half times as frequently. Undoubtedly, many disorders considered and recorded as carcinoma of the head of the pancreas are in reality carcinoma of the extrahepatic bile ducts, and the symptom picture presented by them is mistakenly accepted as pathognomonic of involvement of the head of the pancreas.

For these reasons, it was decided to ignore in this analysis any differentiation into carcinoma of the head and of the body and tail. It was deemed better to gather a broad conception of the symptoms and signs to be expected in all cases of carcinoma of the pancreas as they occur consecutively in a general hospital.

Age.—As is true of carcinoma in general, carcinoma of the pancreas is found in the more advanced age groups. The average age in our 34 cases was 59.4 years, whereas the average age in a collected series of 971 cases was 56.4 years (table 4).

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6. Rienhoff, W. F., and Lewis, D.: Surgical Affections of the Pancreas Met with in the Johns Hopkins Hospital from 1899 to 1932, Including a Report of a Case of an Adenoma of the Islands of Langerhans, and a Case of Pancreatolithiasis, Bull. Johns Hopkins Hosp. **54**:386, 1934.

7. Ransom, H. K.: Carcinoma of the Body and Tail of the Pancreas, Arch. Surg. **30**:584 (April) 1935.

Sex.—Carcinoma of the pancreas characteristically affects men more frequently than women. Men comprised 67.6 per cent of the patients in our 34 cases, whereas in a collected series of 1,120 cases men comprised 71.3 per cent, with a ratio of men to women of approximately 2.4:1 (table 5).

Race.—It is commonly accepted that Negroes are relatively immune to carcinoma of the pancreas. A review of various reports studied from

TABLE 4.—*Age Distribution in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Average Age, Yr.	Age Range	Majority Distribution
1858	Da Costa [8]	37	....	.....	After 40th year
1919	Futcher [9c]	31	....	34-75	96.7% between 41 and 70
1919	Mussey [9a]	90	56.0	.....	.....
1920	Speed, K.: Am. J. M. Sc. **160**:1, 1920..	52	57.0	36-76	.....
1922	Eusterman [9g]	48	56.0	32-74	.....
1924	Cameron [9b]	61	60.4	30-90	.....
1927	Kiefer [9h]	33	56.5	33-76	.....
1928	Friedenwald and Cullen [9i]	37	....	.....	86.4% between 41 and 70
1933	Eusterman and Wilbur [9k]	88	....	.....	72.0% between 40 and 69
1934	Rienhoff and Lewis [6]	100 (mixed)	....	25-74	87.1% between 35 and 64
1935	Ransom [7]	16	57.0	40-69	.....
1937	Rives, Romano and Sandifer [9m].....	96	58.0	25-84	92.5% between 40 and 79
1939	D'Aunoy, Ogden and Halpert [9n].....	40	....	26-80	57.5% over 60
1939	Duff [9c]	50	51.2	18-85	32.0% in 6th decade
1939	Grauer [9k]	34	....	.....	91.1% in 5th to 8th decades
1939	MacKinnon [9q]	47	56.0	31-80	.....
1939	Zollinger and Kevorkian [9r]	40	58.0	.....	.....
1940	Levy and Lichtman [5].....	10	51.8	24-69	.....
1941	Berk	34	59.4	43-91	.....
		971 (595)*	Average 56.4		

* Number of cases in which average age was noted.

the point of view of racial incidence verified the preponderance of the disease in white persons (table 6). Yet in our cases, despite an admission ratio of white persons to Negroes of 3.5:1, the ratio of incidence of carcinoma of the pancreas was only 2.8:1.

SYMPTOMS

Duration of Symptoms.—Carcinoma of the pancreas is a rapidly advancing disease and hence of relatively short duration. In our group of 34 cases and in a collected series of 849 cases the average duration of

symptoms from their first appearance until the time of hospitalization was six months (table 7). In a similar collected series of 759 cases the average duration of symptoms from onset to death was seven and

TABLE 5.—*Sex Distribution in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Males		Females	
1858	Da Costa [5]	37	22		15	
1919	Futcher [2c]	31	22		9	
1919	Mussey [9a]	90	72		18	
1920	Speed, K.: Am. J. M. Sc. **160**: 1, 1920	52	36		16	
1922	Eusterman [2g]	48	35		13	
1924	Cameron [2b]	61	40		21	
1927	Kiefer [2h]	33	18		15	
1928	Friedenwald and Cullen [2i]	37	25		12	
1933	Leven [2l]	99	67		32	
1935	Eusterman and Wilbur [2n]	88	60		28	
1934	Hick and Mortimer [2f]	50	41		9	
1934	Reinhoff and Lewis [6]	109	81		28	
1935	Ransom [7]	16	11		5	
1937	Rives, Romano and Sandifer [2m]	96	78		18	
1939	D'Aunoy, Ogden and Halpert [2a]	40	35		5	
1939	Duff [2c]	50	38		12	
1939	Grauer [2k]	34	26		8	
1939	MacKinnon [2q]	47	23		24	
1939	Zollinger and Kevorkian [27]	49	34		15	
1940	Levy and Lichtman [8]	19	12		7	
1941	Berk	34	23		11	
Total		1,120	No.	%	No.	%
			799	71.3	321	28.7

TABLE 6.—*Racial Incidence in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Whites		Negroes		Admission Ratio Whites
1919	Futcher [2c]	31	30		1		7 : 1
1934	Hick and Mortimer [2f]	50	45		5		Negroes = 38.4% of all autopsies
1937	Rives, Romano and Sandifer [2m]	68	41		27		55 : 45
1939	D'Aunoy, Ogden and Halpert [2a]	40	18		22		.. ..
1939	Duff [2c]	50	36		14		.. ..
1941	Berk	34	25		9		3.5 : 1
Total		273	No.	%	No.	%	
			195	71.4	78	28.6	

one-tenth months (table 7). This would suggest that most patients have a well advanced stage of the disease by the time they seek hospitalization. It also places doubt on the validity of symptoms dating back as far as three years. In such instances the symptoms of the malignant condition of the pancreas have probably merged imperceptibly into those of some preexistent independent gastrointestinal disturbance.

Initial Symptoms and Signs.—In table 8 are presented the initial symptoms and signs observed in a collected series of 379 cases. It is important to note that the outstanding symptom, which was found in one-half the cases, was abdominal pain. Jaundice, the second most fre-

TABLE 7.—*Duration of Symptoms in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Average Duration (Mo.)	Range
	From Onset to Hospitalization			
1922	Eusterman [2g]	90	(Few mo.)	.....
	Eusterman [2g]	48	4.8	.....
1924	Cameron [2b]	61	4.0	11 days to 3 yr.
1927	Kiefer [2h]	33	4.3	10 days to 1 yr.
1928	Friedenwald and Cullen [2i]	37	8.9	3 mo. to 13 mo.
1933	Eusterman and Wilbur [2h]	88	(Less than 6 mo. in 50%)	.....
1934	Marble [2j]	21	12.0	.....
1934	Rienhoff and Lewis [6]	109	...	1 to 12 mo. (87.5%)
1934	Hick and Mortimer [2f]	50	6.9	2 wk. to 3 yr.
1935	Keeton [6m]	17	(3 to 6)	.....
1935	Ransom [7]	16	5.7	Longest duration, 1 yr.
1937	Rives, Romano and Sandifer [2m]	96	4.6	1 wk. to 2 yr.
1938	Ransom [21]	83	5.5	2 wk. to 3 yr.
1939	MacKinnon [2q]	47	3.6	1 mo. to 9 mo.
1940	Levy and Lichtman [5]	19	6.7	3 wk. to 3 yr.
1941	Berk	34	6.0	3 wk. to 3 yr.
		849 (545)*	6.0	
	From Onset to Death			
1927	Kiefer [2h]	31	7.3	.....
1931	Hoffman, F. L.: San Francisco Cancer Survey, Seventh Preliminary Report, Newark, N. J., The Prudential Press, 1931, p. 218	606	10.8	.....
1935	Ransom [7]	16	10.2	.....
1939	D'Aunoy, Ogden and Halpert [2a]	40	4.5	1 mo. to 8 mo.
1939	Duff [2c]	16 (body and tail)	5.0	.....
		16 (head)	4.6	.....
1939	Grauer [2k]	34	...	1 mo. to 7 yr.
		759 (725)*	7.1	

* Number of cases in which average duration of symptoms was noted.

quent initial symptom, was seen in only one fifth of the cases. In our own group, of the 18 cases in which the order of appearance could be definitely established, pain occurred before jaundice in 15 (83.3 per cent), whereas jaundice appeared before pain in only 3. In 10 of the 18 cases the head was felt to be the dominant site involved, and in 9 of these 10 cases pain was present before jaundice. Kiefer [2h] noted that in 16

of 18 cases (88.8 per cent) pain occurred before jaundice. When his cases are combined with ours, it is apparent that in 86.1 per cent of the instances in which both jaundice and pain were present, the pain made its appearance before the jaundice.

TABLE 8.—*Initial Symptoms and Signs in Cases of Carcinoma of the Pancreas*

			Symptom or Sign									
Year	Author	Number of Cases	Pain		Jaundice		Loss of Weight		Anorexia		Gastrointestinal Disturbances (Flatulency, Etc.)	
1933	Eusterman and Wilbur [9h]	88	30		..		..		..		30	
1934	Hick and Mortimer [2f]	46	23		6		6		7		..	
1937	Rives, Romano and Sandifer [2m]	96	58		19		..		..		..	
1938	Ransom [21]	83	30		..		..		..		..	
1939	Duff [2c]	16 (body and tail)	14		0		3		4		6	
		16 (head)	5		13		..		..		..	
1939	Grauer [9k]	34	20		..		..		..		..	
		379	No.	%	No.	%	No.	%	No.	%	No.	%
			189 (379)*	49.8	38 (174)*	21.8	9 (62)*	14.5	11 (62)*	17.7	36 (104)*	34.6

* Number of cases in which the initial symptom or sign was noted.

TABLE 9.—*Chief Complaints in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Pain		Jaundice		Loss in Weight	Anorexia	Weakness	Vomiting	Diarrhea	Constipation
1919	Mussey [9e]	90	40		19		Gastric disorders....22					
1927	Kiefer [2h]	33	9		17		..	..	..	..	..	..
1935	Keeton [9m]	17 (head)	Great majority		..		..	..	..	..	..	..
1935	Ransom [7]	16 (body and tail)	13		..		..	..	..	..	..	..
1940	Berk	34	22		12		1	1	2	3	1	2
			No.	%	No.	%		No.			%	
		190	84 (173)*	48.5	48 (157)*	30.5		32 (124)*			25.8	

* Number of cases in which the complaint was noted.

Chief Complaints.—It is difficult to evaluate chief complaints because of the known effect which pain of any type has on patients. Nevertheless, it is the chief complaints which primarily cause a patient to seek medical attention. It is of great interest, therefore, to note again that abdominal pain was the leading complaint in one half of 190 collected cases (table 9). Jaundice was a chief complaint in less than one

third, and all the other more common complaints combined were presented in only one fourth, of the cases.

Pain.—As early as 1858 Da Costa [8] stressed the frequency (86.5 per cent) of abdominal pain in a collected series of cases of carcinoma of the pancreas, as well as the characteristics of such pain as it occurs in cases of this disease. Many writers since then have repeatedly emphasized that abdominal pain is often the earliest complaint and during the course of the disease forms the most common and the most prominent symptom.[9] Despite this, authors of widely used texts either have described pain as usually absent or unimportant [10] or have devoted but passing attention to it,[11] and current medical thought still clings to the belief that jaundice, usually of a painless nature, is the outstanding and commonest manifestation of carcinoma of the pancreas (table 2).

Eusterman and Wilbur [9h] described the following features as typical of the pain in their patients: epigastric situation, radiation to the back,

8. Da Costa, J. M.: Cancer of the Pancreas, North Am. Med.-Chir. Rev. **2**:883, 1858.

9. (*a*) Bourne, G.: Pain as the Only Sign of Pancreatic Carcinoma, Lancet **2**:1326, 1936. (*b*) Cameron, G.: Carcinoma of the Pancreas in Australia, M. J. Australia **1**:414, 1924. (*c*) Donaldson, M.; Cade, S.; Harmer, W. D.; Ward, R. O., and Edwards, A. T.: The Early Diagnosis of Malignant Disease, London, Oxford University Press, 1936, p. 106. (*d*) Duff.[2e] (*e*) Dunphy, J. E.: The Early Diagnosis of Cancer of the Pancreas, Am. J. Digest. Dis. **7**:69, 1940. (*f*) Elman, R.: Contributions Made in 1939 to Knowledge in Regard to the Pancreas, ibid. **7**:227, 1940. (*g*) Eusterman, G. B.: Carcinoma of the Pancreas: A Clinical Study of One Hundred and Thirty-Eight Cases, Tr. Am. Gastro-Enterol. A. **25**:126, 1922. (*h*) Eusterman, G. B., and Wilbur, D. L.: Primary Malignant Neoplasm of the Pancreas: A Clinical Study of Eighty-Eight Verified Cases Without Jaundice, South. M. J. **26**:875, 1933. (*i*) Friedenwald, J., and Cullen, T. S.: Carcinoma of the Pancreas: Clinical Observations, Am. J. M. Sc. **176**:31, 1928. (*j*) Futcher.[2e] (*k*) Grauer, F. W.: Pancreatic Carcinoma: A Review of Thirty-Four Autopsies, Arch. Int. Med. **63**:884 (May) 1939. (*l*) Hick and Mortimer.[2f] (*m*) Keeton, R. W.: Symptoms of Pancreatic Disease and the Mechanism of Their Production, M. Clin. North America **18**:1297, 1935. (*n*) Kiefer.[2h] (*o*) Leven.[2i] (*p*) Levy and Lichtman.[5] (*q*) MacKinnon, D. C.: Carcinoma of the Pancreas: An Analysis of Forty-Seven Treated Cases from the Lahey Clinic in Boston, Minnesota Med. **22**:281, 1939. (*r*) Mirallié, C.: Cancer primitif du pancréas, Gaz. d. hôp. **46**:889, 1893. (*s*) Mussey, R. D.: Pancreatic Carcinoma, M. Clin. North America **3**:681, 1919; (*t*) Diseases of the Liver, Pancreas and Suprarenal Capsules, in Nothnagel, H.: Encyclopedia of Practical Medicine, authorized translation from the German under the supervision of A. Stengel, Philadelphia, W. B. Saunders Company, 1903, vol. 6, pp. 156 and 168. (*u*) Ranson.[2i] (*v*) Ranson.[7] (*w*) Rienhoff and Lewis.[6] (*x*) Yaskin.[1] (*y*) Zollinger, R., and Kevorkian, A. Y.: Surgical Aspects of Obstructive Jaundice, New England J. Med. **221**:486, 1939.

10. Robson, A. W. M., and Cammidge, P. J.: The Pancreas: Its Surgery and Pathology, Philadelphia, W. B. Saunders Company, 1907, p. 514.

11. Opie, E. L.: Disease of the Pancreas, Philadelphia, J. P. Lippincott Company, 1910, p. 291.

dull aching character, moderate severity, constancy, steady progression, exaggeration at night and nonrelationship to normal events of the digestive cycle. Kiefer [2h] described three main types of pain: (1) a steady, dull, severe midepigastric pain radiating to the lower part of the back; (2) a paroxysmal pain beginning near the umbilicus and radiating widely to the back, to the front of the chest and over the abdomen, and (3) a colicky pain usually occurring in the right hypochondrium and sometimes radiating to the right subscapular region. In any patient all of the types might be seen from time to time. Duff,[2c] on the other hand, expressed the opinion that "there is no constant type or location of pain which is common to all or even to a majority of the cases [of carcinoma of the body or tail of the pancreas], much less any special characteristic of the pain which is peculiar to this disease alone." In our cases all the characters and variations of pain described were exhibited, but we were unable to single out any one common or classic form.

Radiation of the abdominal pain to the back has been remarked on by several observers, who recorded its incidence in percentages ranging from 18 to 50.[12] In some cases lumbar pain is experienced independent of any associated pain in the anterior part of the abdomen. For example, in 1 of our cases the patient was referred to us from the orthopedic department, to which he had been sent because of lumbar pain necessitating the wearing of a brace for three months.

Da Costa [8] called attention to the relief some patients obtained by stooping or by curving their bodies forward. Chauffard [4] described some classic positions assumed by patients to obtain relief from pain which he felt were significantly characteristic of a malignant condition of the pancreas. These positions included sitting up, leaning forward in bed, walking with the body leaning or bending forward at the hips and lying curled up on the right side. Lying in bed or assuming the recumbent position frequently intensified the pain,[13] presumably because this position placed the nervous structures anterior to the vertebral column, especially the solar plexus, under tension. For this reason pain not uncommonly made its first appearance at night and recurred during the night or early morning hours, serving to awaken the patient from sleep. If any feature was outstanding in the pain exhibited in our cases, it was the tendency to appear at night or when a patient was lying down, becoming worse in the back, interfering with sleep and forcing the patient to sit up, bend forward or walk around to secure some relief.

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12. Dunphy.[9e] Eusterman.[9g] Eusterman and Wilbur.[9h] Grauer.[9k] MacKinnon.[9q] Mirallié.[9r] Mussey.[9s] Ransom.[7] Zollinger and Kevorkian.[9y]

13. Bourne.[9a] Cameron.[9b] Dunphy.[9e] Eusterman.[9g] Hick and Mortimer.[2f] Levy and Lichtman.[5] Mirallié.[9r]

The severity of the pain appears to vary, according to the previous reports in the literature. Although most authors agreed that the pain is usually of moderate severity, others described pain of a mild type [9h] or epigastric distress or uneasiness, in contradistinction to real pain.[14] Ransom [2l] expressed the opinion that the most striking characteristic of the pain was its unusual severity, and Hick and Mortimer [2f] described it as severe. In evaluating pain in our cases we discarded such complaints as epigastric discomfort and vague colicky or crampy distress and accepted only pain of such severity as to require specific therapy directed toward its relief alone. We, too, were impressed by the degree of severity of the pain manifested. In a number of cases repeated injections of morphine or related analgesics were required to obtain effectual relief.

A classic ulcer rhythm of pain with partial to complete relief with taking of food which was displayed in 4 of our 34 cases (11.7 per cent) led in these cases to a mistaken early diagnosis of peptic ulcer. Eusterman and Wilbur [9h] described dyspepsia characteristic of ulcer in 12 of 88 cases and Grauer [9k] obtained a typical history of ulcer in 4 of 34 cases. Carcinomatous invasion of the adjacent portions of the stomach and the duodenum and subsequent ulceration are by no means rare in a primary malignant condition of the pancreas [15] and could easily account for symptoms of ulcer. Likewise, in view of the high incidence of peptic ulcer in any cross section of the population, a benign ulceration might be expected as an independent lesion in some cases of carcinoma of the pancreas. In a few cases, however, in which no demonstrable malignant invasion of the stomach or the duodenum or no other lesion was found at necropsy a definite ulcer syndrome was seen during life.[9k] This is a misleading feature, which merits a warning remark.

Pain was present at the time of admission to the hospital in 22 of our 34 cases (64.7 per cent) and appeared at some time during the course of observation in 28, or 82.3 per cent (table 10); such an incidence places this symptom second only to loss of weight in frequency of occurrence. In a collected series of 1,181 cases, pain was present at some time or other in 76.4 per cent (table 10). It can be seen from table 10 that pain was more frequent in cases of carcinoma involving only the body and tail than it was in cases of carcinoma involving only the head. Of our 17 cases in which the head of the pancreas was thought to be the only site involved, pain was present at some time during the course of observation in 13 (76.4 per cent), a frequency practically equal to that of jaundice (14, or 82.3 per cent).

14. Da Costa.[8] Kiefer.[2h]

15. Da Costa.[8] Grauer.[9k] Hick and Mortimer.[2f] Yaskin.[1]

Jaundice.—Attention was previously called to the fact that in approximately 86 per cent of cases pain appeared before jaundice when both symptoms were present and the times of appearance could be deter-

TABLE 10.—*Incidence of Pain at Some Time or Other in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Pain Occurred at Some Time or Other	Percentage
	Cases of Involvement of Head Only			
1930	Duff [2c]	16	12	75.0
1929	Zollinger and Kevorkian [2y]	49	38	77.0
		65	50	Average 76.9
	Cases of Involvement of Body or Tail Only			
1935	Ransom [7]	16	16	100.0
1930	Duff [2c]	16	15	93.7
1940	Levy and Lichtman [5]	19	18	94.6
		51	49	Average 96.1
	Admixed Cases			
1858	Da Costa [8]	37	32	86.5
1893	Mirallié [2r]	113	56	49.5
1919	Mussey [9a]	90	80	88.8
1919	Futcher [2e]	31	25	80.6
1920	Speed, K.: Am. J. M. Sc. **160**: 1, 1920	52	32	61.0
1924	Cameron [9b]	61	43	70.5
1927	Kiefer [2h]	33	21	63.6
1928	Friedenwald and Cullen [9i]	37	31	83.9
1931	Yaskin [1]	4	4	100.0
1933	Leven [2i]	32	32	100.0
1933	Easterman and Wilbur [2h]	88	66	75.0
1934	Rienhoff and Lewis [6]	109	95	87.2
1934	Marble [2j]	21	16	76.1
1934	Hick and Mortimer [2f]	46	43	93.4
1935	Keeton [9m]	17	14	82.3
1936	Bourne [9a]	3	3	100.0
1937	Rives, Romano and Sandifer [2m]	93	72	77.4
1938	Ransom [21]	83	55	66.6
1939	Grauer [9k]	34	20	58.8
1939	MacKinnon [9q]	47	36	76.5
1941	Berk	34	28	82.3
		1,065	804	Average 75.4
	Entire series	1,181	903	Average 76.4

mined. Other observers have noted that jaundice was not an early sign but appeared at various intervals after the onset of symptoms.[16]

16. Ferguson, A. H.: Carcinoma of the Pancreas, Surg., Gynec. & Obst. **10**: 393, 1910. Da Costa.[8] Dunphy.[9e] Grauer.[9k] Keeton.[9m] Shapiro and Lifvendahl.[2n]

At the time of admission to the hospital, jaundice was present in 20 of our 34 cases (58.8 per cent), and in 24 (70.5 per cent) it developed at some time during the course of observation (table 11). This is a

TABLE 11.—*Incidence of Jaundice at Some Time or Other in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Jaundice Present at Some Time or Other	Percentage
	Cases of Involvement of Head Only			
1934	Hick and Mortimer [2f]	22	19	86.3
1939	Zollinger and Kevorkian [9y]	49	42	86.0
1939	Duff [2c]	16	13	81.2
1939	D'Aunoy, Ogden and Halpert [2a]	31	22	70.9
		118	96	Average 81.3
	Cases of Involvement of Body or Tail Only			
1939	Duff [2c]	16	8	50.0
1939	D'Aunoy, Ogden and Halpert [2a]	9	2	22.2
1940	Levy and Lichtman [5]	12	4	33.3
		37	14	Average 37.8
	Admixed Cases			
1858	Da Costa [8]	37	22	59.4
1919	Mussey [9s]	90	37	41.1
1919	Futcher [2e]	29	23	79.3
1920	Speed, K.: Am. J. M. Sc. **160**: 1, 1920	52	42	80.0
1922	Eusterman [9g]	48	22	46.0
1924	Cameron [9b]	61	33	54.1
1927	Kiefer [2b]	33	25	75.7
1928	Friedenwald and Cullen [9i]	37	29	78.4
1933	Eusterman and Wilbur [9h]	403	315	78.1
1933	Leven [9j]	32	21	66.6
1934	Rienhoff and Lewis [6]	109	76	69.7
1934	Hick and Mortimer [2f]	46	23	50.0
1934	Marble [2j]	21	15	71.4
1937	Rives, Romano and Sandifer [2m]	93	72	77.4
1939	Grauer [9k]	34	20	58.8
1939	MacKinnon [9q]	47	28	59.5
1941	Berk	34	24	70.5
		1,206	827	Average 68.5
	Entire series	1,361	937	Average 68.8

definitely lesser incidence than that of pain (64.7 per cent on admission and 82.3 per cent during observation). In a collected series of 1,361 cases jaundice was noted in 68.8 per cent, a definitely lesser incidence than that of pain (76.4 per cent).

As might be expected, jaundice was seen less often in those cases of carcinoma involving only the body and tail of the pancreas (37.8 per cent) than it was in those cases of carcinoma involving only the head (81.3 per cent). It is interesting, however, that in approximately one fifth of all cases of the latter type jaundice was not displayed at any time, and it is even more striking that in 48.8 per cent of the cases in which jaundice never developed the carcinoma was in the head of the pancreas (table 11). This figure compares well with that of Eusterman,[9g] who observed that in 42 per cent of 26 cases in which there was

TABLE 12.—*Incidence of Painless Jaundice at Onset or on Admission in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Painless Jaundice Was Present at Onset of Illness or Admission to Hospital	Percentage
1939	Grauer [9k]	34	3	8.8
1941	Berk	34	9	26.5
		68	12	Average 17.6

TABLE 13.—*Incidence of Painless Jaundice Throughout Course of Observation in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Painless Jaundice Was Present Throughout Course of Observation	Percentage
1919	Mussey [9s]	90	6	6.6
1937	Rives, Romano and Sandifer [9m]	93	18	19.3
1941	Berk	34	6	17.6
		217	30	Average 13.8

no jaundice the head of the pancreas was involved. As was noted before, of our 17 cases in which the head was felt to be the only site involved jaundice was displayed in 14, or 82.3 per cent, at some time during the course of observation, which incidence is but slightly greater than that of pain (13, or 76.4 per cent).

Painless Jaundice.—Completely contrary to the popular conception of painless jaundice as the classic symptom of carcinoma of the pancreas are the figures shown in tables 12 and 13. It was previously indicated that pain was far and away the commonest initial symptom and was the dominant feature during the course of pancreatic carcinoma. It is not surprising, then, to find, as have several other

investigators,[17] that jaundice without any associated pain is a phenomenon which is not encountered with any great frequency.

Since all forms of mild discomfort were ignored, painless jaundice was felt to be present at the time of admission in 26.5 per cent of our 34 cases but was seen in only 17.6 per cent of a combined series of 68 cases (table 12). Since the incidence of pain increased during the course of observation, the incidence of persistent painless jaundice decreased during the observation period to 17.6 per cent in our cases and to 13.8 per cent in a collected series of 217 cases (table 13).

TABLE 14.—*Incidence of Loss in Weight in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Loss in Weight Occurred	Percentage	Average Loss in Weight (Lb.)	Average Rate of Loss in Weight (Lb. per Week)
1919	Futcher [2e]	31	29	93.5	..	..
1920	Speed, K.: Am. J. M. Sc. **160**: 1, 1920	52	47	90.0	..	..
1922	Eusterman [9c]	90	..	....	26	..
	Eusterman [9c]	48	..	....	29	..
1924	Cameron [9b]	61	43	70.5	..	..
1927	Kiefer [2h]	33	28	84.8	28	5
1933	Leven [21]	32	32	100.0	..	10
1934	Rienhoff and Lewis [5]	109	94	86.2	..	..
1934	Hick and Mortimer [2f]	46	43	93.4	..	..
1934	Marble [21]	21	18	85.7	..	..
1935	Ransom [7]	16	16	100.0	..	5.25
1937	Rives, Romano and Sandifer [2m]	56	50	89.2	..	..
1939	D'Aunoy, Ogden and Halpert [2s]	40	Practically all	....	..	..
1939	Duff [2c]	16 (body and tail)	16	100.0	..	..
		16 (head)	Majority	....	..	..
1939	MacKinnon [9q]	47	40	85.1	22.7	..
1939	Zollinger and Kevorkian [27]	49	41	86.0	....	(7 per mo.)
1940	Levy and Lichtman [5]	19	16	84.2	..	..
1941	Berk	31	28	90.1	..	..
		813 (619)*	541	Average 87.4	26.4	6.8

* Total number of cases in which loss of weight was noted.

Loss of Weight.—Loss of weight is the most frequent symptom found in cases of carcinoma of the pancreas. It was present in 90.1 per cent of our cases at the time of admission and was noted at some time during the illness in 87.4 per cent of a collected series of 813 cases (table 14). The loss of weight in cases of this disease is characteristically rapid and great. In the same series of collected cases the total loss averaged 26.4 pounds (11.9 Kg.), with an average loss of 6.8 pounds (3.1 Kg.) per week (table 14).

17. Dunphy.[9e] Grauer.[9k] Leven.[21] Mussey.[9s] Ransom.[21] Shapiro and Lifvendahl.[2n]

Fatigue and Weakness.—Associated with the prominent loss of weight and with cachexia are fatigue and weakness. These were noted at the time of admission in 78.3 per cent of our cases and at some time in 51.1 per cent of a collected series of 186 cases (table 15).

Anorexia.—Loss of appetite was a complaint at the time of admission in 40.9 per cent of our cases and at some time in 44.4 per cent of a collected series of 290 cases (table 16).

TABLE 15.—*Incidence of Fatigue and Weakness in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Fatigue and Weakness Was Present	Percentage
1927	Kiefer [2b]	33	21	63.6
1934	Marble [2j]	21	9	42.8
1934	Rienhoff and Lewis [6]	109	47	43.1
1941	Berk	23	18	78.3
		186	95	Average 51.1

TABLE 16.—*Incidence of Anorexia in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Anorexia Was Present	Percentage
1858	Da Costa [8]	25	7	28.0
1924	Cameron [9b]	61	17	27.9
1927	Kiefer [2b]	33	20	60.6
1934	Marble [2j]	21	6	28.5
1934	Hick and Mortimer [2f]	46	30	65.0
1935	Ransom [7]	16	3	18.7
1939	MacKinnon [9q]	47	19	82.9
1940	Levy and Lichtman [5]	19	18	94.7
1941	Berk	22	9	40.9
		290	129	Average 44.4

Nausea and Vomiting.—Nausea alone, vomiting alone or nausea and vomiting together occurred in 42.3 per cent of a collected series of 759 cases (table 17). In several of our own cases and in a number of the cases reported by others, persistent vomiting could be attributed to obstruction of the pylorus or the duodenum by the malignant growth in the pancreas. Because of the ease with which these areas lend themselves to encroachment and compression by pancreatic tumors, it is not surprising that in some patients intestinal obstruction is one of the earliest manifestations of a primary pancreatic neoplasm.

Constipation.—Constipation is a fairly common and often an early complaint in cases of carcinoma of the pancreas. In 43.3 per cent of our cases the patients were constipated for the first time in their lives when they were admitted to the hospital or were much more severely constipated than they had ever been previously. Constipation of like character was present at some time in 38.7 per cent of a collected series of 573 cases (table 18).

TABLE 17.—*Incidence of Nausea and Vomiting in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Symptom Was Present	Percentage
	Nausea Alone			
1927	Kiefer [25b]	33	20	60.6
1934	Hick and Mortimer [25f]	46	10	21.7
1939	MacKinnon [25q]	47	10	21.3
1941	Berk	23	11	47.8
		149	51	Average 34.2
	Vomiting Alone			
1858	Da Costa [5]	37	21	56.7
1919	Futcher [26]	31	10	32.2
1924	Cameron [25b]	61	23	37.7
1934	Hick and Mortimer [25f]	46	16	34.8
1939	MacKinnon [25q]	47	13	17.0
1939	Zollinger and Kevorkian [27]	49	18	37.0
1940	Levy and Lichtman [5]	19	2	10.5
1941	Berk	31	13	41.9
		321	116	Average 36.1
	Nausea and Vomiting			
1933	Leven [21]	32	18	56.0
1934	Bienhoff and Lewis [6]	109	72	66.1
1934	Marble [23]	21	9	42.8
1937	Rives, Romano and Sandifer [25m]	98	44	47.3
1939	Grauer [28]	34	11	32.3
		289	154	Average 53.2
	Entire series	759	321	Average 42.3

Diarrhea.—Diarrhea, usually of an intermittent character, proved to be a not infrequent symptom in cases of carcinoma of the pancreas. At the time of admission diarrhea was or had been present in 30 per cent of our 34 cases, although in a collected series of 679 cases it was present in only 10.8 per cent (table 19). Its frequency as a symptom in cases of carcinoma of the pancreas is, therefore, one third that of constipation. This is in sharp contrast to the ratio of constipation to diarrhea in routine office practice, which is approximately

10:1. Friedenwald and Cullen [91] called attention to a small group of cases in which definite signs were preceded by persistent diarrhea. The authors expressed the belief that this occurs frequently enough to

TABLE 18.—*Incidence of Constipation in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Constipation Was Present	Percentage
1858	Da Costa [8]	34	19	55.8
1920	Speed, K.: Am. J. M. Sc. **160**:1, 1920	52	19	36.5
1924	Cameron [9b]	61	25	40.9
1927	Kiefer [3b]	33	16	48.4
1934	Hick and Mortimer [2f]	46	17	36.9
1934	Rienhoff and Lewis [6]	109	30	27.5
1935	Ransom [7]	16	13	81.2
1937	Rives, Romano and Sandifer [3m]	93	31	33.0
1938	Ransom [21]	83	(28+)	33.3+
1939	Duff [3c]	16	11	68.7
1941	Berk	30	13	43.3
		573	222	Average 38.7

TABLE 19.—*Incidence of Diarrhea in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Diarrhea Was Present	Percentage
1858	Da Costa [8]	34	3	8.8
1919	Futcher [3e]	31	1	3.2
1920	Speed, K.: Am. J. M. Sc. **160**:1, 1920	52	3	5.7
1924	Cameron [9b]	61	8	13.1
1927	Kiefer [3b]	33	0	0.0
1928	Friedenwald and Cullen [91]	37	6	16.2
1934	Marble [3j]	21	4	19.0
1934	Hick and Mortimer [2f]	46	1	2.1
1934	Rienhoff and Lewis [6]	109	5	4.6
1935	Keeton [9m]	30	5	16.6
1937	Rives, Romano and Sandifer [3m]	93	19	20.0
1938	Ransom [21]	83	10	12.5
1940	Levy and Lichtman [5]	19	0	0.0
1941	Berk	30	9	30.0
		679	74	Average 10.8

warrant the conclusion that whenever persistent diarrhea which cannot be accounted for by the usual causes is observed in a person during middle life carcinoma of the pancreas should be suspected. In 2 of our cases intermittent diarrhea heralded the appearance of other signs and symptoms.

Nervous Phenomena.—Yaskin [1] first called attention to the presence in cases of pancreatic carcinoma of early symptoms which were largely psychic. Latter and Wilbur [18] and Dunphy [9e] reported similar cases. The essential features described by Yaskin consisted of: anxiety; obstinate insomnia not ascribable to pain or relieved by the usual somnifacients; depression, with crying spells, conviction of imminent physical danger; absence of feelings of unreality, and absence of disturbances in perception, memory, orientation or judgment. The importance of appreciating that such mental phenomena occur rests on the fact that patients who experience them are invariably labeled as psychoneurotic when they complain of abdominal pain or of pain in the back in addition to their psychic symptoms. The true condition goes unsuspected until jaundice makes a belated appearance, at which time little can be done therapeutically.

One of Yaskin's cases was reported from this hospital, and, exclusive of that case, psychic phenomena of the type described were seen in 3 of our 34 cases.

PHYSICAL FINDINGS

Palpable Liver.—Bard and Pic [3] stressed that the liver of a patient with carcinoma of the head of the pancreas was characteristically not enlarged. The liver was palpable in over three fourths (78.8 per cent) of our cases and in almost two thirds (63.2 per cent) of a collected series of 454 cases (table 20). It cannot be said, of course, that all livers which are barely palpable are always enlarged. Rives and his associates [2m] noted that of 41 cases in which necropsy was done the liver appeared enlarged clinically in 51 per cent, while enlargement was apparent at necropsy in only 21 per cent. Furthermore, concomitant jaundice and hepatic metastasis affect in varying degree the size of the liver and the ease with which it can be felt. Nevertheless, the fact that so many livers can be felt casts doubt on the truth or value of the classic impression that the liver is not enlarged in cases of carcinoma of the head of the pancreas.

Distended Gallbladder.—A time-honored concomitant of the traditional painless jaundice described in cases of carcinoma of the pancreas is distention of the gallbladder in accordance with the law of Courvoisier. A distended gallbladder could be felt clinically in 41.6 per cent of our 24 cases with associated jaundice (table 21), and in one fourth (24.2 per cent) of all 34 cases, including those with and those without associated jaundice, was an enlarged gallbladder found on

18. Latter, K. A., and Wilbur, D. L.: Psychic and Neurologic Manifestations of Carcinoma of the Pancreas, Proc. Staff Meet., Mayo Clin. **12**:457, 1937.

physical examination. In a collected series of cases a distended gallbladder could be demonstrated clinically in one half (50.9 per cent) of 175 cases with associated jaundice (table 21) and one third (37.5 per cent) of 729 cases with or without associated jaundice. The number of

TABLE 20.—*Incidence of Palpable Liver in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Liver Was Palpable	Percentage
1919	Futcher [2c]	31	12	38.7
1924	Cameron [9b]	61	29	47.5
1927	Kiefer [2b]	33	26	78.9
1928	Friedenwald and Cullen [21]	37	17	45.9
1933	Leven [21]	32	26	81.0
1937	Rives, Romano and Sandifer [2m]	93	61	65.5
1939	Duff [2c]	32	23	71.8
1939	Grauer [9k]	34	15	44.1
1939	Zollinger and Kevorkian [27]	49	39	80.0
1940	Levy and Lichtman [8]	19	13	68.4
1941	Berk	33	26	78.8
		454	287	Average 62.2

TABLE 21.—*Incidence of Distended Gallbladder in Cases of Carcinoma of the Pancreas with Jaundice*

Year	Author	Number of Cases	Number in Which Gallbladder Was Palpable Clinically	Percentage	Number in Which Gallbladder Was Found Distended at Laparotomy or Necropsy	Percentage
1919	Mussey [9a]	37	..	....	31	83.7
1922	Eusterman [9g]	22	11	50.0	20	90.9
1927	Kiefer [2b]	23	15	65.2	..	....
1933	Leven [21]	20	14	70.0	..	....
1939	Duff [2c]	21	6	28.5	..	....
1939	MacKinnon [9q]	28	..	....	25	89.2
1941	Berk	24	10	41.6	..	....
		175 (110, clinically)	56	Average 50.9 (87, laparatomy or necropsy)	76	Average 87.3

gallbladders found distended at the time of operation or autopsy, however, was much greater than the number which could be felt on examination. In the collected series, evidence of distention of the gallbladder was obtained at laparotomy or necropsy in 87.3 per cent of the 175 cases with associated jaundice (table 21) and in 66.6 per cent of the 729 cases with or without associated jaundice. Courvoisier's law, there-

fore, would appear to be of even more value to the surgeon at the time of operation than to the clinician during the physical examination.[21]

Pancreatic Mass.—The retroperitoneal location of the pancreas renders that organ relatively inaccessible to ordinary palpation. In a number of instances we could feel abdominal masses in the general area that the pancreas might be expected to occupy, but, accepting only instances in which other possible sites were fairly well excluded, we could definitely feel a pancreatic mass in only 12.1 per cent of cases (table 22). Of a collected series of 707 cases, a pancreatic mass was said to have been palpated in 37.3 per cent (table 22).

TABLE 22.—*Incidence of a Palpable Pancreatic Mass in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Pancreatic Mass Was Palpable	Percentage
1858	Da Costa [6]	37	13	35.1
1919	Futcher [2a]	31	12	38.7
1919	Mussey [9a,c]	90	50	56.0
1922	Eusterman [9c]	48	20	41.6
1924	Cameron [9b]	61	23	37.7
1927	Kiefer [2b]	33	9	27.2
1928	Friedenwald and Cullen [21]	37	16	43.2
1933	Leven [21]	32	7	21.8
1933	Eusterman and Wilbur [9b]	88	52	59.1
1935	Ransom [7]	16	8	50.0
1938	Ransom [21]	85	32	38.5
1939	Duff [2c]	16	2	12.5
1939	Grauer [9k]	34	2	5.8
1939	Zollinger and Kevorkian [27]	49	5	9.0
1940	Levy and Lichtman [5]	19	9	47.3
1941	Berk	33	4	12.1
		707	264	Average 37.3

A number of investigators have called attention to the fact that pancreatic masses may be movable, despite their deep position.[19] We were able to confirm this in 2 cases.

Ascites.—Ascites may develop in cases of pancreatic carcinoma as a result of metastases into the peritoneum or into the liver, hypoproteinemia, thrombosis of the portal vein or compression of the portal vein by lymph nodes or by malignant tissue. Whether the ascitic fluid is hemorrhagic or clear depends on its cause. As might be expected, ascites was found with greater frequency at operation or at autopsy (35.2 per

19. Eusterman and Wilbur.[9b] Friedenwald and Cullen.[21] Kiefer.[2b] Levy and Lichtman.[5]

cent) (table 23) than it was clinically (15.6 per cent). It was felt to be present clinically in 4 of our 34 cases (11.7 per cent). When the cases in which ascites was observed clinically and those in which it was found at operation or necropsy were combined, it was found that ascites was reported in 23.7 per cent of 737 cases (table 23).

TABLE 23.—*Incidence of Ascites in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Ascites Was Present	Percentage
	Preoperative or Antemortem Diagnosis			
1893	Mirallié [2r]	113	13	11.5
1919	Futcher [2e]	31	4	12.9
1920	Speed, K.: Am. J. M. Sc. 160:1, 1920	52	10	20.0
1922	Eusterman [2s]	22	4	18.1
1924	Cameron [2b]	61	10	16.4
1927	Kiefer [2h]	33	3	9.0
1933	Leven [2i]	32	7	21.8
1934	Marble [2j]	21	6	28.5
1935	Keeton [2m]	30	6	20.0
1941	Berk	34	4	11.7
		429	67	Average 15.6
	Postoperative or Postmortem Diagnosis			
1922	Eusterman [2s]	22	10	45.4
1933	Leven [2i]	99	48	48.4
1934	Hick and Mortimer [2f]	46	8	17.4
1935	Ransom [7]	16	3	18.7
1939	Duff [2c]	32	11	34.3
1939	Grauer [2k]	34	8	23.5
1939	D'Aunoy, Ogden and Halpert [2a]	40	14	35.0
		289	102	Average 35.2
	Basis of Diagnosis Not Definitely Stated			
1940	Levy and Lichtman [6]	19	6	31.5
	Entire series	737	175	Average 23.7

LABORATORY DATA

Disturbed Carbohydrate Metabolism.—Glycosuria: Glycosuria as a manifestation of disturbed carbohydrate metabolism in cases of carcinoma of the pancreas has been appreciated for a long time. Nevertheless, the frequency with which this has been reported is definitely greater since 1928 than before that time. This is a reflection, perhaps, of an increasing recourse to laboratory tests as instruments of diagnosis. Glycosuria was present prior to operation or necropsy in 24.2 per cent of our cases, whereas in only 9.4 per cent of a collected series of 692 cases was

glycosuria evidenced at some time (table 24). The collected series dates back to 1893, however, and includes the low percentages of the earlier reports.

Hyperglycemia: Hyperglycemia occurred with about the same frequency (27.3 per cent) in our cases as did glycosuria (table 25). In

TABLE 24.—*Incidence of Glycosuria in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Glycosuria Was Present	Percentage
1893	Mirallié [9r]	50	13	26.0
1919	Futcher [3e]	31	3	9.7
1919	Mussey [9s]	90	4	4.4
1920	Speed, K.: Am. J. M. Sc. **160**: 1, 1920	52	3	5.7
1922	Eusterman [9t]	48	5	10.4
1924	Cameron [9b]	61	2	3.3
1927	Kiefer [3j]	33	2	6.0
1928	Friedenwald and Cullen [9l]	37	6	16.0
1933	Leven [3l]	32	3	9.3
1935	Keeton [9m]	30	3	10.0
1935	Ransom [7]	16	2	12.5
1937	Rives, Romano and Sandifer [3m]	96	2	2.0
1938	Ransom [3l]	83	9	10.7
1941	Berk	33	8	24.2
		692	65	Average 9.4

TABLE 25.—*Incidence of Hyperglycemia in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Hyperglycemia Was Present	Percentage
1933	Leven [3l]	32	5	15.6
1935	Rives, Romano and Sandifer [3m]	96	9	9.3
1935	Keeton [9m]	30	6	20.0
1938	Ransom [3l]	35	6	17.1
1939	Grauer [9k]	14	8	57.1
1940	Levy and Lichtman [8]	12	6	50.0
1941	Berk	33	9	27.3
		252	49	Average 19.4

the collected series, on the other hand, hyperglycemia was twice as frequent (19.4 per cent of 252 cases) as glycosuria. The data on hyperglycemia, it should be pointed out, were drawn from reports made between 1933 and 1940, years during which the reported incidence of glycosuria was also definitely greater.

Impaired Dextrose Tolerance: Impairment of carbohydrate metabolism seems to be best revealed by means of a dextrose tolerance test.

We have encountered instances, just as have others reporting on the subject, in which there was neither glycosuria nor hyperglycemia, yet in which a definitely impaired tolerance to dextrose could be demonstrated. In our hands the test has yielded a surprisingly high percentage (77.8) of positive results in the cases in which it has been employed (table 26), and we have come to rely on the demonstration of impaired dextrose tolerance as of great diagnostic importance in cases of suspected carcinoma of the pancreas. The experience of other investigators has varied, so that in only 20.8 per cent of a collected group of 163 cases was an impaired tolerance to dextrose displayed (table 26). Nevertheless, this figure represents a greater incidence than that recorded for either glycosuria or hyperglycemia alone.

TABLE 26.—*Incidence of Impaired Dextrose Tolerance in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Impaired Dextrose Tolerance Was Present	Percentage
1922	Eusterman [9z]	48	5 (approximately)	10.4 (approximately)
1928	Friedenwald and Cullen [9i]	4	4	100.0
1934	Hick and Mortimer [2f]	46	8	17.8
1935	Ransom [7]	16	1	6.2
1938	Ransom [21]	35	6	17.1
1939	Grauer [9k]	2	1	50.0
1940	Levy and Lichtman [5]	3	2	66.6
1941	Berk	9	7	77.8
		163	34	Average 20.8

In this regard, Marble,[2j] after a review of the literature on carbohydrate metabolism in nondiabetic patients with carcinoma, concluded that the bulk of evidence seems to indicate that in a large percentage of cases of carcinoma of any type, certain rather slight, though definite abnormalities in sugar tolerance curves are obtained. Reduced intake of food, metastases to the liver, the hepatic changes incident to prolonged biliary obstruction and potential diabetes are factors which act independently of the carcinoma itself to influence dextrose tolerance. We witnessed in 1 case the return of a normal dextrose tolerance curve after cholecystogastrostomy, and in a number of other cases the degree of impairment of carbohydrate metabolism seemed less after palliative operations that in no way affected the primary neoplasm itself.

Combined Defects in Carbohydrate Metabolism: Of our cases in which suitable determinations were made, both glycosuria and hypo-

glycemia were present in 18.2 per cent (6 of 33), a combination of glycosuria, hyperglycemia and impaired dextrose tolerance in 33.3 per cent (3 of 9), and glycosuria or hyperglycemia or an impaired dextrose tolerance curve in 41.8 per cent (14 of 33). These figures illustrate the diagnostic value of some demonstrable defect in carbohydrate metabolism in cases of suspected pancreatic carcinoma.

Precedent Diabetes Mellitus.—In a number of cases in which some form of defective carbohydrate metabolism was demonstrated diabetes was known to exist. The predisposing role of diabetes mellitus in cases of carcinoma of the pancreas has long attracted speculative attention but is still a mooted problem. A number of investigators have expressed the belief that any association between the two conditions is purely coincidental [20] and is probably to be explained by the fact that both

TABLE 27.—*Incidence of Precedent Diabetes Mellitus in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Precedent Diabetes Mellitus Was Present	Percentage
1924	Cameron [2b]	61	1	1.6
1933	Loven [21]	32	2	6.2
1934	Hick and Mortimer [2f]	46	3	6.5
1938	Ransom [21]	83	6	7.2
1940	Levy and Lichtman [5]	19	3	15.7
1941	Berk	34	4	11.7
		275	19	Average 6.9

diseases have their maximum incidence in the same age groups. Marble,[2j] on the contrary, found that of 256 malignant conditions in 10,000 persons proved to have diabetes 33, or 13 per cent, were carcinoma of the pancreas, and McKittrick and Root [2k] found that 32.4 per cent of 37 malignant conditions in 2,179 persons proved to have diabetes were carcinoma of the pancreas. The pancreas was far and away the most common site of a malignant condition in these diabetic patients, and the aforementioned percentages (13 and 32.4) indicate a distinctly greater incidence than that of pancreatic carcinoma in the population at large (1 to 2 per cent of all carcinomas).

In 11.7 per cent of our cases there was a history of long-standing diabetes mellitus, while in 6.9 per cent of a collected series of 275 cases there was a history of such a condition (table 27).

20. Kiefer.[2b] Ransom.[21]

Anemia.—Despite the rapid wasting and the cachexia displayed in cases of carcinoma of the pancreas, it is remarkable how slight an anemia is present. This fact is in marked contrast to the usual finding in cases of a malignant condition of the gastrointestinal tract in general and might prove of some value in the differential diagnosis of these two types of lesions. In 75.8 per cent of our cases the red cell count was less than 4,500,000 per cubic millimeter of blood at the time of admission to the hospital (table 28). In only 32.4 per cent of a collected series of 292 cases was anemia displayed, although the several reports varied in the severity of criteria. The average red cell count in our cases was 4,080,000, and in the collected series 4,040,000 per cubic millimeter

TABLE 28.—*Incidence of Anemia in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Anemia Was Present	Percentage	Average Red Cell Count, Millions	Average Hemoglobin Concentration, Percentage
1927	Kiefer [2h]	22	9 (less than 4,000,000 red cells)	42.8	.....	....
1933	Eusterman and Wilbur[2h]	88	12 (approximately)	13.0+	.....	....
1933	Leven [21]	32	..	....	.....	79.4
1935	Ransom [7]	16	..	....	.....	75.0
1938	Ransom [21]	83	..	....	4,000,000	74.0
1940	Levy and Lichtman [8]	18	..	....	.....	80.7
1941	Berk	33	25 (less than 4,500,000 red cells)	75.8	4,080,000	69.5
		292 (142)*	46	Average 32.4	4,040,000	75.7

* Total number of cases in which anemia was noted.

of blood. The concentration of hemoglobin tended to run lower than the red cell counts, which discrepancy resulted in hypochromia. The average hemoglobin concentration was 69.5 per cent in our cases and 75.7 per cent in the collected series (table 28).

Roentgenologic Findings.—The roentgenogram has proved of inestimable value in establishing the diagnosis of pancreatic carcinoma prior to operation. The data in table 29 demonstrate how the accuracy of roentgenologic diagnosis and the percentage of positive findings have increased in recent years.

In our experience the most common signs of a malignant condition of the pancreas were: (1) obstruction at some part of the duodenum, usually the third part, or at the pylorus, with stasis in the proximal parts; (2) irregularity and deformity of the pylorus and the duodenum from infiltrative encroachment, and (3) widening of the sweep of the duodenum.

In 14, or 45.2 per cent, of the 31 of our cases in which roentgenograms of the gastrointestinal tract were made, there were changes which warranted the roentgenologist's suggestion that a malignant condition existed in or about the pancreas (table 29). If we were to include, in addition, those cases in which no mention was made of a malignant condition at the time of the examination but in which, in retrospect, suggestive signs were apparent, the number in which there were positive findings would be increased to 20, or 64.5 per cent. Positive findings were noted in 37 per cent of a collected series of 367 cases (table 29).

TABLE 29.—*Incidence of Positive Roentgen Ray Findings in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Positive Roentgen Ray Findings Were Present	Percentage
1920	Speed, K.: Am. J. M. Sc. **160**: 1, 1920	23	2	8.7
1927	Kiefer [2b]	13	0	0.0
1933	Leven [21]	24	6	25.0
1933	Eusterman and Wilbur [9b]	68	32	47.0
1935	Ransom [7]	15	4	26.6
1937	Rives, Romano and Sandifer [2m]	50	23	46.0
1938	Ransom [21]	93	24	25.8
1939	Duff [2c]	20	10	50.0
1939	MacKinnon [9a]	21	15	71.4
1940	Levy and Lichtman [6]	9	6	66.6
1941	Berk	31	14	45.2
		367	136	Average 37.0

Pancreatic Enzymes in Blood.—Johnson and Bockus [21] have incorporated into a recent report their experiences in the study of diseases of the pancreas by means of determining serum lipase concentrations. According to their technic, values of serum above 1 cc. of a twentieth-normal solution of sodium hydroxide are indicative of some abnormal condition in the pancreas. Determinations of serum lipase were made by them in 11 of the 34 cases of malignant conditions of the pancreas analyzed in this report. Concentrations in excess of 1 cc. of a twentieth-normal solution of sodium hydroxide were obtained in 6 cases. In 4 cases the abnormal levels were obtained prior to operation and in 2 only after the diagnosis had been established at operation. The preoperative positivity, therefore, was 36.1 per cent, and the positivity

21. Johnson, T. A., and Bockus, H. L.: Diagnostic Significance of Determinations of Serum Lipase, Arch. Int. Med. **66**:62 (July) 1940.

of the test at some time or other in the course of the disease was 54.5 per cent. Comfort and Osterberg,[22] using a little higher standard for normal lipasemia (1.5 cc. of a twentieth-normal solution of sodium hydroxide), recently reported 40.5 per cent accuracy for elevations of serum lipase and 8.0 per cent accuracy for elevation of serum amylase in cases of carcinoma of the pancreas. These simple determinations, particularly the concentration of serum lipase, hold forth much promise as diagnostic aids in cases of pancreatic carcinoma. A greater percentage of positivity will probably be obtained as the tests are done more frequently and earlier in cases of suspected carcinoma of the pancreas.

Bloody Stools.—The absence of blood in stools has been advanced as an aid in the differential diagnosis of pancreatic carcinoma and carcinoma of the gastrointestinal tract, with which the former might be confused. As a matter of fact, this criterion is not entirely reliable. Although gross bleeding in cases of carcinoma of the pancreas is uncommon, it has been reported.[23] Requiring that two or more stools yield plus 3 or stronger reactions to the Gregerson test before they were considered positive for occult blood, we were able to find occult blood in the stools in 26.9 per cent of our cases (table 30). Of a collected series of 424 cases blood was found in the stools in 27.5 per cent (table 30).

Fatty Stools.—Large, bulky, fermenting, fatty, greasy or buttery stools are traditionally associated with carcinoma of the pancreas. Actually, however, such stools are rare. Defining a fatty stool as one either macroscopically fatty in appearance or one exhibiting microscopically a plus 4 reaction for neutral fat, fatty acids or soap on two or more occasions, we were able to find fatty stools before operation or necropsy in only 4 per cent of our cases. Although in 9.7 per cent of a collected series of 680 cases (table 31) fatty stools were displayed at some time, the other diagnostic criteria in many instances were such that the mere presence of microscopic amounts of fat was sufficient to warrant the stools being designated as fatty. Coffey, Mann and

22. Comfort, W. W., and Osterberg, A. E.: The Value of Determination of the Concentration of Serum Amylase and Serum Lipase in the Diagnosis of Disease of the Pancreas, Proc. Staff Meet., Mayo Clin. **15**:427, 1940.

23. Adler, F. H.: Carcinoma of the Pancreas with Ulceration into the Gastro-Intestinal Tract, J. A. M. A. **76**:158 (Jan. 15) 1921. Duff.[2e] Eusterman.[2g] Ochsner, H. C., and Wilbur, D. L.: Malignant Lesions Involving the Duodenum as a Causative Factor in Gastro-Intestinal Hemorrhage, Proc. Staff Meet., Mayo Clin. **9**:776, 1934. Secousse: Un cas de cancer du pancréas chez un sujet jeune avec terminaison par hémorrhagie intestinale, J. de méd. de Bordeaux **44**:507, 1914. Troisier, J.; Bariéty, M., and Gabriel, P.: Hématémèse par bourgeonnement intraportal d'un cancer pancréatique, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:368, 1934. Yaskin.[1]

Bollman [24] were able to demonstrate in dogs that gross alterations of the digestive functions appear only in the complete absence of the external pancreatic secretion and small amounts of pancreas are adequate

TABLE 30.—*Incidence of Blood in Stools in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Blood Was Present in Stools	Percentage
1858	Da Costa [8]	34	3	8.8
1920	Speed, K.: Am. J. M. Sc. **160**: 1, 1920	52	16	30.0
1927	Kiefer [2b]	27	10	37.0
1933	Leven [21]	16	6	37.5
1934	Rienhoff and Lewis [6]	109	23	21.1
1935	Ransom [7]	8	4	50.0
1938	Ransom [21]	109 (only 83 with primary carcinoma of pancreas)	34	31.1
1939	Duff [2c]	32	12	37.5
1940	Levy and Lichtman [5]	11	2	18.1
1941	Berk	26	7	26.9
		424	117	Average 27.5

TABLE 31.—*Incidence of Fatty Stools in Cases of Carcinoma of the Pancreas*

Year	Author	Number of Cases	Number in Which Fatty Stools Were Present	Percentage
1858	Da Costa [8]	34	3	8.8
1868	Mirallié [9r]	113	9	7.9
1919	Futcher [2e]	31	17	54.8
1920	Speed, K.: Am. J. M. Sc. **160**: 1, 1920	52	8	15.0
1924	Cameron [9b]	61	1	1.6
1927	Kiefer [2b]	33	7	21.2
1928	Friedenwald and Cullen [9i]	37	8	21.6
1933	Leven [21]	32	9	28.1
1934	Marble [2j]	21	3	14.2
1934	Hick and Mortimer [2f]	46	0	0.0
1935	Ransom [7]	16	0	0.0
1937	Rives, Romano and Sandifer [2m]	96	0	0.0
1938	Ransom [21]	83	0	0.0
1941	Berk	25	1	4.0
		660	66	Average 9.7

to maintain complete digestion. Complete failure of fat digestion, with resultant fatty stools of the greasy type, would be expected, therefore,

24. Coffey, R. J.; Mann, F. C., and Bollman, J. L.: The Influence of the Pancreas on the Utilization of Foodstuffs, Am. J. Digest. Dis. **7**:144, 1940.

only in a few cases of severe and advanced disease in which there was complete destruction of functioning pancreatic tissue.

CONCLUSIONS

Diagnostic accuracy in cases of carcinoma of the pancreas is only about 25 to 30 per cent, despite the need for early and accurate diagnosis.

A good part of this lack of diagnostic efficiency is attributable to persistent false impressions as to the usual picture presented by carcinoma of the pancreas.

Overlapping of the areas anatomically involved is so great in carcinoma of the pancreas that it is better to consider the symptoms presented irrespective of the dominant site affected rather than to divide them into those of carcinoma of the head and those of carcinoma of the body and tail.

A review of 34 cases of carcinoma of the pancreas seen at the Graduate Hospital of the University of Pennsylvania and verified by laparotomy or necropsy justifies the following conclusions:

1. Carcinoma of the pancreas is a disease of fairly rapid progression (an average of six months from onset of symptoms to hospitalization) which occurs mostly in persons in the sixth and seventh decades (average age, 59.4 years) and affects mostly men (67.6 per cent) and white persons (73.5 per cent), although Negroes appear to be proportionately more prone to the disease than white persons (white persons:Negroes = 2.8:1, with an admission ratio of 3.5:1).

2. Pain is the outstanding chief complaint (in 64.7 per cent) and occurs at some time or other during the course of the disease more frequently (in 82.3 per cent) than does jaundice (70.5 per cent). Even in those cases in which the head of the pancreas is the dominant site involved pain will be present at some time during the course of observation just about as often as will jaundice (13 and 14 cases, respectively, in this series). When both jaundice and pain are present, the pain will precede the jaundice in approximately 85 per cent of cases. This was true in 90 per cent of our 10 cases in which the head was the dominant site of involvement.

3. The pain has no constant features common to a large majority but may be continuous and dull, paroxysmal or colicky; it is usually severe; it frequently radiates into the back and may be limited to the back; it is characteristically worse at night when a patient is lying down but is relieved by sitting up or walking about, and it may adopt an ulcer-like rhythm.

4. Although painless jaundice is a symptom complex of unquestionable diagnostic importance, it is not encountered with any great

frequency. One fourth (26.5 per cent) of all patients at the time of admission present painless jaundice, and it persists in one sixth (17.6 per cent) during the period of observation.

5. Whereas the head is nearly always invaded by the carcinomatous process when jaundice is present (20 out of 21 cases in which the parts affected could be determined), jaundice need not necessarily occur when the head is involved. In three tenths (10 out of 34, or 29.5 per cent) of all cases jaundice never developed, and in at least 60 per cent of these cases the head was definitely known to be involved.

6. Loss in weight is the most commonly noted symptom (90.1 per cent) and is usually rapid and severe. Weakness (78.3 per cent), nausea (47.8 per cent), vomiting (41.9 per cent) and anorexia (40.9 per cent) are associated symptoms which occur fairly frequently.

7. Constipation is found more often (43.3 per cent) than diarrhea (30 per cent). The ratio of occurrence of these symptoms (1.4:1), however, is much less than the usual ratio seen in routine office practice. Diarrhea, therefore, must be looked on as a symptom of some import in cases of suspected carcinoma of the pancreas.

8. The gallbladder can be felt on physical examination in four tenths (41.6 per cent) of those cases with associated jaundice and in one fourth (24.2 per cent) of all cases of carcinoma of the pancreas. Courvoisier's law is even more valuable to the surgeon at operation than to the clinician at the time of physical examination.

9. The liver is palpable in over three fourths (78.8 per cent), a pancreatic mass can be felt in one eighth (12.1 per cent) and ascites is demonstrable clinically in about one ninth (11.7 per cent) of all cases of a malignant condition of the pancreas in which the patient is seen in a hospital.

10. Some derangement of carbohydrate metabolism is an important diagnostic finding in cases of suspected pancreatic carcinoma. It may manifest itself in the form of an impaired dextrose tolerance curve (77.8 per cent), as hyperglycemia (27.3 per cent) or as glycosuria (24.2 per cent). All three of these defects could be demonstrated in one third (33.3 per cent) and either one of the three was found in four tenths (41.8 per cent) of all cases of carcinoma of the pancreas in this series.

11. Anemia (less than 4,500,000 red cells per cubic millimeter of blood) is seen in three fourths (75.8 per cent) of all cases but is strikingly mild (4,080,000 red cells and a hemoglobin concentration of 69.5 per cent as an average).

12. The roentgenogram is a most important adjunct in diagnosis. An initial diagnosis of a malignant condition in or about the pancreas

can be established by roentgen ray studies in almost one half the cases (45.2 per cent).

13. The determination of concentrations in the blood of such pancreatic enzymes as lipase and amylase offers a new diagnostic aid of real value. The concentration of serum lipase can be demonstrated to be abnormally great in over one third (36.1 per cent) of all cases prior to operation and in approximately 50 per cent at some time during the course of observation.

14. Occult blood in the stools can be demonstrated in one fourth (26.9 per cent) of all cases and its presence may be misleading when one is considering the differential diagnosis of this disease.

15. Fatty stools are uncommon (4 per cent).

It is necessary to revise the present concept of carcinoma of the pancreas. The major role of pain, the importance of demonstrating some impairment of carbohydrate metabolism and the value of the roentgenogram and of determinations of pancreatic enzyme concentration in the blood must be given due note. The traditional picture of painless jaundice and palpable distended gallbladder is seen in 25 to 40 per cent of cases and when present, of course, is significant, but unfortunately, in the majority of cases this syndrome is not presented. Fatty stools are rare.

SUMMARY

A poll was taken among 120 recent medically trained persons, representing thirty-four medical schools, on the question of their impressions of the outstanding diagnostic criterion of carcinoma of the pancreas. Jaundice was selected by 92.5 per cent (111) as the outstanding and commonest feature of the disease, and nearly half of this number specified further that the jaundice was painless. Only 2.5 per cent felt that pain ranked as the predominant characteristic.

An analysis was made of 34 cases of primary carcinoma of the pancreas proved by laparotomy or necropsy, and the results were combined with similar reviews previously reported in the literature.

Pain was shown to occur earlier and more frequently than jaundice and was the outstanding symptom. Painless jaundice proved to occur relatively infrequently.

Some derangement in carbohydrate metabolism, abnormalities in roentgenograms and elevated concentrations of pancreatic enzymes in the blood are findings of invaluable aid in the diagnosis of carcinoma of the pancreas.

In the combined analysis of our 34 cases and those already reported in the literature the following general features of the incidence of

carcinoma of the pancreas were noted: average age 56.4 years; men 71.3 per cent, with a ratio of men to women of 2.4:1; white persons 71.4 per cent, with a ratio of white persons to Negroes of 2.5:1; average duration of symptoms from onset to hospitalization six months, and average duration of illness from onset to death seven and one-tenth months.

In the same analysis the signs and symptoms of carcinoma of the pancreas occurred with the following frequencies:

Symptom	Occurrence, Percentage
Pain as an initial symptom	49.8
Pain as a chief complaint	48.5
Pain at some time during the course of the disease	76.4
Jaundice as an initial symptom	21.8
Jaundice as a chief complaint	30.5
Jaundice at some time during the course of the disease	68.8
Painless jaundice at the time of admission to the hospital	17.6
Painless jaundice throughout the course of observation	13.8
Loss of weight, with an average loss of 26.4 pounds (11.9 Kg.), and an average rate of loss of 6.8 pounds (3.1 Kg.) per week	87.4
Fatigue and weakness	51.1
Anorexia	44.4
Nausea and/or vomiting	42.3
Constipation	38.7
Diarrhea	10.8

Physical Finding	Occurrence, Percentage
Palpable liver	63.2
Palpable, distended gallbladder with associated jaundice	50.9
Palpable distended gallbladder, all cases	37.5
Palpable pancreatic mass	37.3
Ascites occurring preoperatively or antemortem	15.6
Ascites, all cases	23.7

Laboratory Finding	Occurrence, Percentage
Glycosuria	9.4
Hyperglycemia	19.4
Impaired dextrose tolerance	20.8
Anemia with an average red cell count of 4,040,000 and an average hemoglobin concentration of 75.7 per cent	32.4
Positive roentgenologic signs	37.0
Hyperlipasemia	40.0-60.0
Bloody stools	27.5
Fatty stools	9.7

Dr. Henry L. Bockus, professor of gastroenterology, Graduate School of Medicine, University of Pennsylvania, gave advice and criticism during this study.

PRIMARY PULMONARY VASCULAR SCLEROSIS

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Primary pulmonary vascular sclerosis in the restricted sense of the term defined by Brenner [1] is a rare condition. Up to 1935 Brenner collected from the literature only 15 cases, to which he added 1 of his own. This number, however, is probably incomplete; at least 1 other case should be included, the one reported by MacCallum.[2]

Since 1935 2 additional instances have been reported; including the case herein presented, there are now on record some 20 cases fulfilling the requirements for inclusion within this restricted group.

These requirements are (1) the presence of significant hypertrophy of the right ventricle but not of the left and (2) the absence of all factors commonly believed to cause secondary pulmonary vascular sclerosis, pulmonary hypertension or isolated strain of the right side of the heart.

REPORT OF A CASE

A married woman aged 21 entered the Multnomah County Hospital Feb. 2, 1940 because of dyspnea and pain in the chest. She had been moderately short of breath on exertion "all her life," but during the last two years dyspnea became increasingly severe and for the past several months she experienced paroxysms of dyspnea and orthopnea even while at rest, especially at night.

Although she had been told by a physician that she was a "blue baby" at birth and was under the impression that she had always had "heart trouble," no evidence of congenital or any other heart disease was noted on numerous observations in this clinic prior to September 1938, only a little more than one year before her death. Her first appearance at the clinic was in 1931, when she was 12 years of age. Her complaint then was of a "sore throat," and a general examination revealed large tonsils and adenoids. The heart was recorded as normal. Between 1931 and 1938 she was seen on numerous occasions for various and sundry conditions, including pregnancy in 1936, when she was delivered of a healthy baby after a normal, uneventful period of gestation. Many of these observations included

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1. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, Arch. Int. Med. **56**:976-1014 (Nov.) 1935.

2. MacCallum, W. G.: Obliterative Pulmonary Arteriosclerosis, Bull. Johns Hopkins Hosp. **49**:37-48 (July) 1931.

complete physical examinations, and, with the exception of one notation concerning "substernal pulsations," the heart was invariably described as normal; the statement "no murmurs heard" often appeared on the record.

In September 1938, one year and four months before her final admission, she entered the hospital because of dyspnea, vomiting, headache and hemoptysis, and for the first time the question of congenital heart disease came up for consideration. At that time the following significant history was elicited: On slight exertion she often suffered severe dyspnea, cyanosis, precordial pain without radiation, dizziness and fainting spells. She had several attacks of hemoptysis but no cough. She had had scarlet fever at the age of 4 but gave no history of rheumatic fever.

Examination revealed cyanosis, "widening of the heart" with "filling of the waist" and a markedly accentuated pulmonic second sound. Largely on these find-

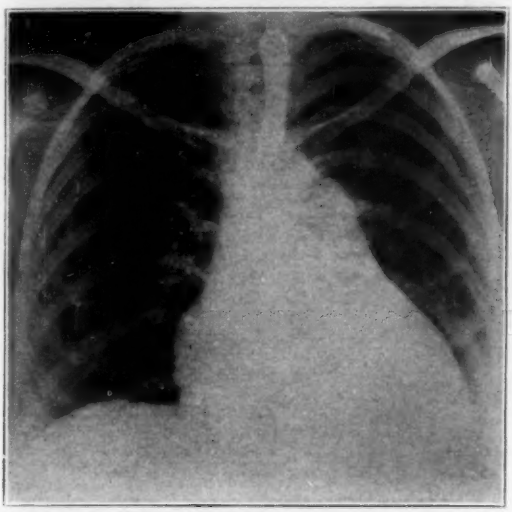

Fig. 1.—Roentgenogram taken nine days before death, showing marked dilatation of the pulmonary artery and conus.

ings, together with roentgenographic evidence of a prominent pulmonary conus, a diagnosis of congenital heart disease was seriously considered, although no murmurs of any sort were heard. Despite the dyspnea, clear lung fields were found on both physical and roentgen examination. It was also noted that there was "no increase in venous pressure." The arterial pressure was 85 systolic and 70 diastolic and was "difficult to get." The basal metabolic rate was —14 per cent. Examination of the blood showed the hemoglobin concentration was 122 per cent, the erythrocyte count 5,700,000 and the leukocyte count 17,550, with 68 per cent neutrophils. The erythrocyte sedimentation rate was 1 mm. for fifteen minutes and 3 mm. for forty-five minutes. The Wassermann, Kahn and Klein reactions were all negative.

The electrocardiogram disclosed the following changes indicative of pronounced right ventricular strain: namely, marked right axis deviation; tall and sharply

spiked P waves, especially in lead II; inversion of the T wave in lead III, and inversion of the T wave without inversion of the QRS complex in lead IV.

The patient's final admission to the hospital was on Feb. 2, 1940. During the preceding year she was under more or less continuous observation in the outpatient department. She complained of increasing dyspnea, palpitation, precordial pain, headache, dizziness, vertigo, fainting spells and attacks of nausea and vomiting. Slight edema of the ankles had developed during the previous two or three months.

Examination at this time disclosed diffuse cyanosis of the face and lips, with malar flush, and deep cyanosis of the nail beds. The heart appeared moderately

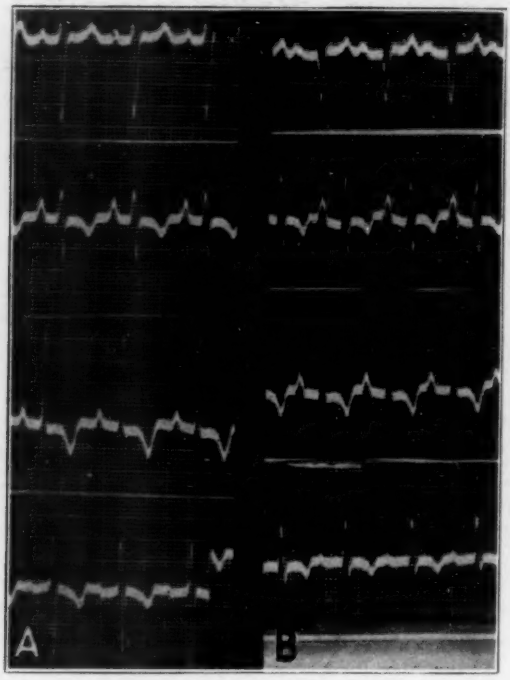

Fig. 2.—Electrocardiograms taken (*A*) September 1938 and (*B*) February 1940, showing marked right axis deviation, tall and sharply spiked P waves and inversion of the T waves in leads II, III and IV, without inversion of the QRS complex in lead IV.

enlarged, with a strong, forceful apex beat about 11 cm. to the left of the midsternal line. The pulmonic second sound was greatly accentuated, but there were no murmurs. The blood pressure was 90 systolic and 75 diastolic. The lung fields were clear throughout. The liver was just palpable below the costal margin, and there was no dependent edema. The roentgenogram of the chest confirmed the clearness of the lung fields and the moderate cardiac enlargement noted clinically. It also disclosed extreme prominence of the pulmonary artery and conus. The

electrocardiographic tracings, the blood counts and other laboratory data were essentially like those previously described.

Clinical Diagnosis.—When the history as just related was presented on Feb. 8, 1940, at one of the regular medical conferences, it appeared clear that the clinical picture was one of severe isolated right-sided heart strain, or primary cor pulmonale. It was also evident from the physical and roentgenologic examinations that no ordinary pathologic condition of the lungs, such as emphysema or pulmonary fibrosis, existed to account for such strain. Mitral stenosis was excluded

Fig. 3.—Anterior view of the heart. The arrow (*A*) indicates the lateral boundaries of the right ventricle. The anterior incision passes through the right ventricle and the center of the pulmonary conus. The entire apex is formed by the right ventricle. Note the small size of the left ventricle (*B*) as compared to that of the right ventricle (*A*) and the striking difference between the right atrial appendage (*C*) and the left atrial appendage (*D*).

with reasonable certainty by the absence of pulmonary engorgement and by the roentgenographic demonstration of a small left auricle. Furthermore, the complete absence of murmurs and thrills and the normal cardiac findings recorded in the numerous observations prior to September 1938 furnished ample evidence against congenital cardiac disease. Because of these considerations a diagnosis was made of primary pulmonary vascular sclerosis.

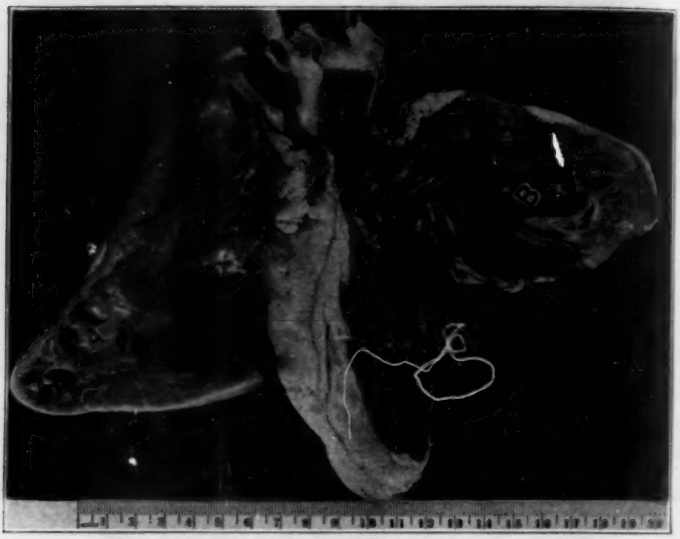

Fig. 4.—Heart opened to show the relative size of the cardiac chambers. The hypertrophy and dilatation of the right ventricle (*A*) and the lack of corresponding change in the left ventricle (*B*) are readily apparent.

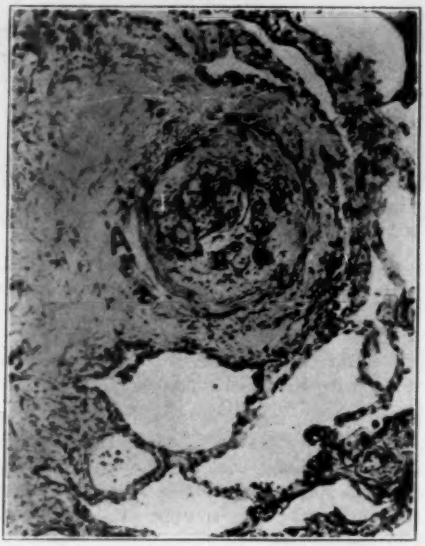

Fig. 5.—A small pulmonary artery (*A*) showing a canalized thrombus.

Four days later, during which interval her condition had remained essentially unchanged, the patient died suddenly.

Gross Postmortem Examination.—The body was that of a well developed and well nourished white woman. Slight cyanosis was apparent in the nail beds and the lips. The chest was symmetric. There was no edema.

The abdominal cavity contained between 100 and 200 cc. of free serosanguineous fluid; the peritoneal surfaces were smooth and shiny. The liver extended 5 cm. below the xiphoid process. The spleen did not extend below the costal margin. No abnormalities were noted in the gastrointestinal tract.

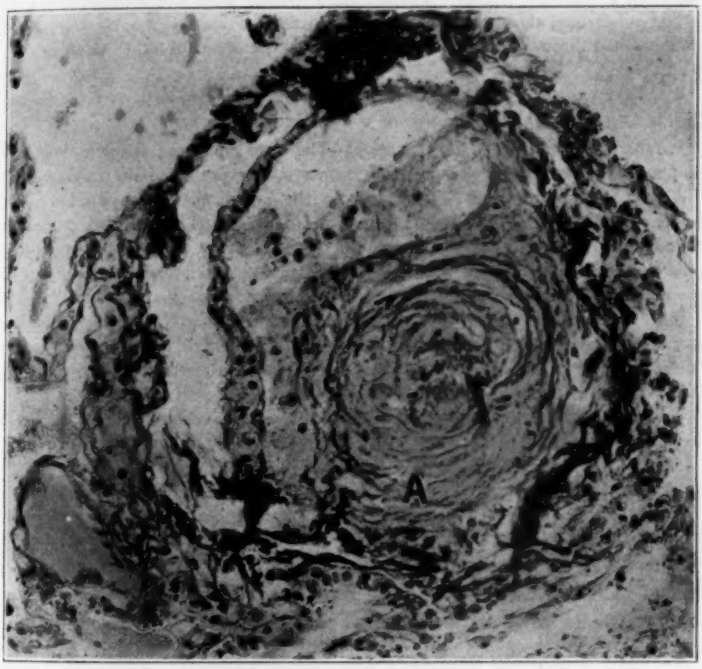

Fig. 6.—A small pulmonary artery (*A*) which has been the seat of a proliferative intimal change, with narrowing of the lumen and subsequent occlusion.

There was no fluid in either pleural cavity. The lungs were pinkish, voluminous and crepitant. The bronchi were dissected and opened as far as the tertiary branches and were found to be normal. On section the pulmonary parenchyma appeared homogeneous; no consolidations or other gross abnormalities were seen. The pulmonary arteries were dissected as far as the tertiary branches; the formation of occasional atherosclerotic plaques was noted.

The pericardial sac contained only a few cubic centimeters of free clear yellow fluid and presented a smooth, shiny inner surface. The heart was enlarged; the maximum transverse diameter was 13 cm., and the weight was 690 Gm. The

enlargement and increased weight were due entirely to dilatation and hypertrophy of the right auricle and ventricle. The left chambers were distinctly small. The size of the right ventricle was more than twice that of the left, and the right auricle was about six times as large as the corresponding left chamber. The myocardium of the right ventricle at the tip and the base measured, respectively, 7.5 and 7 mm. in thickness; the corresponding regions in the left ventricle measured 7 mm. each. The pulmonary artery and conus were extremely prominent. The circumference of the pulmonary valve measured 8.5 cm. and that of the aortic valve 6 cm.; the tricuspid valve measured 12 cm. and the mitral valve 10 cm.

No congenital cardiac defects were present; the foramen ovale was anatomically patent but functionally closed. The coronary vessels were free from sclerosis.

The eviscerated thoracic cage presented no deformities. The aorta was small; it was opened throughout its entire length, and no sclerosis or other changes were found.

The liver was moderately enlarged and was the seat of mild passive congestion. All other abdominal and pelvic organs were essentially normal.

Microscopic Postmortem Examination.—The only significant changes concerned the pulmonary vessels. The lung parenchyma proper presented no abnormalities. The most striking changes were found in the arterioles and capillaries. The majority of the arterioles presented intimal proliferation, which resulted in marked narrowing or complete occlusion of the lumens. The muscularis showed no corresponding hypertrophy. In many of the small arterioles there were present thrombi of various ages. In some instances recanalization had occurred. Many of the capillaries were completely obliterated and hyalinized. The extent of the arteriolocapillary obliteration was such as to indicate a high degree of obstruction within the pulmonary circuit. The larger and medium-sized arteries showed no changes other than the formation of occasional atherosclerotic plaques.

Sections of the liver showed slight dilatation of the venous sinuses and slight swelling of the liver cells.

Sections of the spleen, kidneys and adrenal glands showed no abnormalities.

No significant sclerosis was present in any of the systemic vessels examined.

Comment.—This case in the highest degree fulfils the requirements for a diagnosis of primary pulmonary vascular sclerosis. The outstanding clinical picture was that of severe right-sided heart strain, resulting in death; pathologically marked isolated cor pulmonale was present, and the sole lesion which might bear a causative relation to this fatal cor pulmonale was extensive sclerosis and occlusion of the pulmonary vascular tree. No other possible known cause of right-sided heart strain was present, even in the slightest degree.

The mechanism of death merits comment. Only slight evidence of congestive heart failure was noted either clinically or pathologically. However, more than a year prior to death the patient, while yet under 20 years of age, began to suffer attacks of precordial pain. Sometimes the pain was described as "not radiating," and the attacks were often associated with cyanosis. This association suggests similarity to the "hypercyanotic angina" which has been described, especially by the older writers on so-called Ayerza's disease, as occurring occasionally in severe

grades of chronic cor pulmonale. Although pathologically the coronary vessels were patent and singularly free of sclerosis, it appears highly probable that the final event of sudden death as well as the earlier attacks of anginal pain was due to acute coronary insufficiency arising from a greatly diminished volume of blood delivered to the left ventricle through the obstructed pulmonary circulation. The probable mechanism involved in this type of death was discussed in an earlier communication [3] describing a case of "subacute cor pulmonale" in which a similar death occurred.

SUMMARY OF PREVIOUSLY REPORTED CASES

CASE 1 (Mönckeberg [4]).—A woman aged 33 complained of nervousness and anemia. Examination revealed an enlarged heart, with a systolic and a diastolic murmur over the apex and a systolic murmur over the base, more prominent over the pulmonic area. The blood pressure was 125 systolic. Death occurred after four months with signs of increasing heart weakness. At autopsy there was found pronounced widening of both primary branches of the pulmonary artery. The heart was distinctly enlarged, chiefly because of hypertrophy of the right chambers. The left ventricle appeared as an appendage to the right one.

Microscopically there was sclerosis of the pulmonary arteries, which became diffuse in the branches of the second and third order. In the small branches the intima was four times the thickness of the media. The lung parenchyma was normal.

CASE 2 (Rössle [5]).—Increasing dyspnea and palpitation developed in a woman aged 20. Death occurred at the end of two years. An antemortem diagnosis of congenital heart disease was made.

At autopsy the large branches of the pulmonary artery showed no change, but all the branches with a diameter of 0.5 to 0.4 cm. revealed many yellowish nodules and plaques. There were enormous hypertrophy and dilatation of the right cardiac chambers. The left side of the heart appeared as a mere appendage of the right. No valvular or other structural lesions were present.

Microscopic examination disclosed newly laid down, fine elastic elements in the arteries. The thickened intima in the middle-sized vessels was distinctly fatty in character. The lung parenchyma was normal.

CASE 3 (Sanders [6]).—No clinical findings or impressions were reported. At necropsy the smaller branches of the pulmonary artery were considerably stiffer and thicker than normal. The right ventricle was enormously hypertrophied.

Microscopically the branches of the pulmonary artery 4 to 5 mm. in diameter showed the intima to be thicker than the media. This was due to an increase in connective tissue and in the elastic elements. The lung parenchyma showed no significant change.

3. Brill, I. C., and Robertson, T. D.: Subacute Cor Pulmonale, Arch. Int. Med. **60**:1043-1057 (Dec.) 1937.

4. Mönckeberg, J. G.: Ueber die genuine Arteriosklerose der Lungenarterie, Deutsche med. Wchnschr. **33**:1243-1246 (Aug. 1) 1907.

5. Rössle, R.: Ueber Hypertrophie und Organkorrelation, München. med. Wchnschr. **55**:377-381 (Feb. 25) 1908.

6. Sanders, W. E.: Primary Pulmonary Arteriosclerosis with Hypertrophy of the Right Ventricle, Arch. Int. Med. **3**:257-262 (April) 1909.

CASE 4 (Schütte [7]).—A woman aged 74 died with a condition diagnosed as cardiac insufficiency, with edema, ascites and pleural effusion. No detailed clinical history was given.

At autopsy the lungs were grossly normal. The heart was definitely enlarged. The right ventricle, especially the pulmonary conus, was greatly dilated and hypertrophied.

Microscopically the small branches of the pulmonary artery showed marked intimal thickening. No change was present in the larger vessels. There were generalized anasarca and hydropericardium.

CASE 5 (Ljungdahl [8]).—A woman aged 36 complained of shortness of breath and palpitation. After a few months there developed swelling of the abdomen, which was progressive and later became associated with swelling of the feet.

On physical examination she presented marked ascites but no peripheral edema while resting in bed. The heart was enlarged to the right and left, and forceful pulsation was seen and felt to the left of the lower part of the sternum. A systolic murmur was heard at the apex but was most intense in the third intercostal space. The pulmonary first sound was absent and was replaced by a loud systolic murmur; the second sound was soft and was accompanied by a rough diastolic murmur. A systolic murmur was also heard at the aortic area. There were pallor and slight cyanosis of the lips. A Talma operation was performed for the ascites, but the patient did not improve and died of progressive decompensation.

At postmortem examination the pulmonary veins were seen to be strikingly narrow. The pulmonary artery 8 cm. above the valve showed a thickened intima. In the main branches likewise there was a high grade sclerotic process with many cartilage-like plaques in the intima, resulting in narrowing of the vessels. Branches of the second and third order had a thin, delicate intima and were not grossly altered. The right auricle and right ventricle were extremely enlarged. The myocardium measured 8 mm. in thickness. The left ventricle was small and appeared as an appendage to the right. Its wall measured 11 to 12 mm. in thickness.

Microscopically the trunk and main stem arteries revealed hyperplasia of the connective tissue of the intima, with no elastic tissue but many fat globules. The thickness of the connective tissue varied from 0.32 to 0.88 mm. This change was confined to the trunk and main branches; no changes were found in the smaller branches.

Other findings included ascites and chronic passive congestion.

CASE 6 (Hart [9]).—A woman aged 30 was admitted to the hospital with high grade cyanosis, severe dyspnea and a laboring heart, with murmur.

At necropsy the lungs were grossly normal. The main stem of the pulmonary artery was almost twice as wide as the aorta, but the walls were not thickened. Raised yellow plaques were present on the intima, with wrinkling in between; there were also single, split pea–sized places which were calcified. In the branches

7. Schütte, H.: Rechtsseitige Herzhypertrophie hervorgerufen durch eine entzündliche Veränderungen der kleinen Lungenarterien, Centralbl. f. allg. Path. u. path. Anat. **25**:483-485, 1914.

8. Ljungdahl, M.: Untersuchungen über die Arteriosklerose des kleinen Kreislaufs, Wiesbaden, J. F. Bergmann, 1915.

9. Hart, C.: Ueber dis isolierte Sklerose der Pulmonalarterie, Berl. klin. Wchnschr. **53**:304-306 (March 20) 1916.

the intima showed many yellowish white flecks, with raised furrows between. A spreading adherent thrombus was found in the right pulmonary artery. The heart was approximately twice the normal size, chiefly because of enlargement of the right chambers. The apex was formed by the right ventricle. The pulmonary conus was greatly hypertrophied.

CASE 7 (Hart [9]).—A woman aged 25 had been under a physician's care for a cardiac condition for six months. After this period she was bedridden for three weeks, with marked dyspnea, cyanosis and forceful pounding of her heart.

On physical examination she presented cyanosis, edema of the ankles, pulsating, distended jugular veins and a thrill over the apex of the heart. Systolic and diastolic murmurs were heard over the apical and pulmonary areas. The radial pulse was small, and its rate was slow. She died suddenly.

At autopsy the pulmonary artery and branches were of normal width; in the smaller vessels the intima had yellowish white plaques. There was hypertrophy of the right ventricle and atrium with atrophy of the left ventricle. The apex of the heart was formed by the right ventricle.

In this case, as in the preceding one (case 6), no detailed microscopic observations were given, but in the discussion the author implied that significant microscopic changes were present.

CASE 8 (Krutzsch [10]).—A man aged 26, for whom no clinical history was included, was found at autopsy to have lungs of deep brown color, with edema and atelectasis at the bases. The main stem of the pulmonary artery had a smooth intima, except for occasional thickening. The branches of the first order were corrugated and showed fine thickenings. There were striking thickenings in the branches of the second and third order and in the smaller branches.

The heart was greatly enlarged, chiefly because of hypertrophy and dilatation of the right ventricle. The myocardium of the right ventricle was 12 mm. thick at the conus. The wall of the left ventricle was 11 mm. thick. The circumference of the pulmonary artery was 8 cm., of the aorta 6.5 cm. and of the tricuspid valve 14 cm.

Microscopically the arteries and arterioles showed a thickened intima, composed of loose, fine connective tissue with some proliferation of the elastic tissue. There were numerous lymphocytes in some and occasional strands of hyaline connective tissue in others. Fat droplets were present in some areas of thickening.

Other findings included anasarca, cyanosis of the face, hydropericardium and chronic passive congestion of the liver, spleen and kidneys.

CASE 9 (Krutzsch [10]).—A man aged 23, for whom no clinical history was available, was found at necropsy to have sharply circumscribed reddish brown areas which stood out above the surface in the lower lobes of both lungs. The larger pulmonary vessels showed yellowish thickenings of the intima. In the medium-sized arteries there were plaques of confluent character; in the smaller branches there were many more such plaques.

The heart was greatly enlarged, because of great increase in size of the right ventricle; the left ventricle appeared merely as an appendage. The wall of the right ventricle measured 9 mm. in thickness at the conus: the wall of the left one

10. Krutzsch, G.: Ueber rechtsseitige Herzhypertrophie durch Einengung des Gesamtquerschnittes der kleineren und kleinsten Lungenarterien, Frankfurt. Ztschr. f. Path. **23**:247-271, 1920.

measured 10 mm. in thickness. The circumference of the aorta was 7 cm., of the pulmonary artery 8 cm., of the mitral valve 11 cm. and of the tricuspid valve 14 cm.

Microscopic lesions were apparently identical with those described in case 8; the one description was given by the author as applicable in both cases.

Other findings included cyanosis of the face, hands and finger nails and chronic passive congestion of the viscera.

CASE 10 (Eppinger and Wagner [11]).—A man aged 50 complained of swelling of the lower extremities, shortness of breath, anorexia, hoarseness and fulness of the neck. These symptoms were of one year's duration; one month before death there developed edema and cough.

On physical examination there were found cyanosis, distention of the veins of the neck, edema of the dependent portions, slight dyspnea, hoarseness, signs of atelectasis at the bases of the lungs, enlargement of the heart on percussion with accentuated pulmonic sounds, ascites and an enlarged, pulsating liver. The roentgenogram and electrocardiogram showed hypertrophy of the right side of the heart. The red blood cell count was 6,320,000.

A diagnosis was made of primary vascular disease of the pulmonary artery.

At autopsy the lungs were compressed focally. They were deeply pigmented. The pulmonary artery and all its branches were grossly normal. The right side of the heart was enlarged to twice the normal size; the left ventricle was small. The thickness of the wall of the left ventricle was scarcely 1 cm.; that of the wall of the right ventricle was more than 1 cm.

Microscopically there was marked thickening of the smallest vessels. The intima was thickened in a plaquelike manner, which resulted in some areas in complete occlusion. The changes were diffuse.

Other findings included general cyanosis, anasarca, chronic passive congestion of the viscera and a broadened, flabby, thin-walled aorta.

CASE 11 (Tschistowitsch [12]).—A woman aged 38, whose chief complaints were of edema of the feet and dyspnea, was found on physical examination to have pronounced hypertrophy of the right side of the heart, intense cyanosis, edema of the feet and dyspnea. There were no other cardiac signs. A diagnosis was made of "pulmonary arteriosclerosis with marked emphysema." She died in two months, without responding to the administration of heart-stimulating drugs.

At autopsy the lungs were normal, with no gross sclerosis of the pulmonary arteries. There was pronounced hypertrophy of the right side of the heart.

Microscopically marked intimal thickening of the small arteries, with thrombosis in many, was apparent. Many arteries were completely occluded, as were many of the capillaries.

CASES 12 and 13 (Goedel [13]).—Two men aged 59 and 50, respectively, entered the hospital, each with a picture of rapidly developing heart failure. They

11. Eppinger, H., and Wagner, R.: Zur Pathologie der Lunge, Wien. Arch. f. inn. Med. **156**:83-146, 1920.

12. Tschistowitsch, T.: Thrombo-endoartérite pulmonaire chronique, Compt. rend. Soc. de biol. **89**:627, 1923.

13. Goedel, A.: Zur Kenntnis der Hypertrophie des rechten Herzens und schwerer Kreislaufstörung infolge Verödung der Lungenschlagaderperipherie, Virchows Arch. f. path. Anat. **277**:507-521, 1930.

presented dyspnea, marked cyanosis and distressing cough, but no edema. In both the condition was diagnosed as "myocardial degeneration."

At autopsy in each instance there were marked enlargement and dilatation of the right ventricle. The left side of the heart appeared atrophic. The valves were intact. In the first case the lungs were congested and slightly edematous. There was a thrombus in the main stem of the pulmonary artery, which continued through both main branches into the middle-sized arteries, occluding many. Microscopically the thrombus was old and partially organized. There were areas of thickening of the intima with partially hyalinized connective tissue. The terminal arteries revealed intimal hyperplasia, with thrombus formation and often recanalization.

In the second case the lungs were congested but not edematous. An occasional middle-sized artery was occluded by thrombosis. A slight amount of lipoid flecking and streaking was also seen in the intima.

Microscopically the small arteries showed the most change, which consisted of intimal proliferation with narrowing of the lumen, thrombus formation and recanalization. There were injected capillary-like vessels in the periadventitia, in the peribronchial tissue and in the bronchial submucosa.

CASE 14 (MacCallum [2]).—A Negro housewife aged 39 complained of pain in the stomach and shortness of breath. At 24 she began to be breathless on exertion. One year later she began to have fainting attacks, always associated with undue physical exertion. One year ago, at 38 years of age, when she was hospitalized for an operation on the uterus, her heart seemed normal except for a systolic murmur to the left of the sternum and an accentuated second pulmonic sound. Four months ago the old symptoms, including cough and tightness about her heart, returned, with increased severity.

Examination revealed a temperature of 100 F., a pulse rate of 125 per minute, a respiratory rate of 24 per minute, a blood pressure of 125 systolic and 95 diastolic, dyspnea, moderate cyanosis and enlarged, pulsating neck veins. The lungs were normal. The heart was much enlarged to the right and to the left; sounds were loud, especially the pulmonic second sound; a marked presystolic gallop, a loud first sound, a soft systolic murmur and a faint mid-diastolic murmur were heard at the apex. There was slight edema of the extremities. The Wassermann reaction of the blood was negative. The electrocardiogram showed pronounced right axis deviation. The heart grew progressively weaker. Finally, with nausea, dyspnea, delirium and pain in the chest and the epigastrium, she lost consciousness and died.

At autopsy there were found arteriosclerosis and arteriolosclerosis of the pulmonary arteries, with secondary thrombosis and organization of the thrombi. The formation of plaques and the thickening were limited to the intima; the media and adventitia were fairly normal. While all the pulmonary arteries were involved, the process was most marked in those arterioles which measured much less than 1 mm. in diameter.

The heart was greatly enlarged, wholly because of hypertrophy and dilatation of the right auricle and ventricle. No valvular or other structural defects were seen.

The lung tissue in general was surprisingly free from disease.

CASE 15 (Kuntschik [14]).—A 15 year old girl, whose chief complaint was hemoptysis, had suffered with heart trouble for the previous ten or eleven years and

14. Kuntschik, R.: Zur Kenntnis der sogenannten primären Pulmonalsklerose, Ztschr. f. Kreislaufforsch. **23**:183-198 (March 15) 1931.

had been unable to do heavy work. She was feeble, listless and often short of breath, but the dyspnea was never of a high grade. Fever and bloody sputum developed a week before she was hospitalized. She was thought to have tuberculosis and was put to bed, but the cultures of the sputum, which continued to be blood tinged, were negative for tubercle bacilli. Cough, cyanosis and tachycardia continued. Death was sudden.

At autopsy the lungs were somewhat collapsed, and the lower lobe of the left lung contained an infarct. In the branches of the main pulmonary artery and in the secondary vessels there were raised, yellowish white atherosclerotic lesions. Marked narrowing was present in the medium and small vessels. The heart was enlarged, and the apex was formed by the right ventricle. The left ventricle appeared as an appendage to the right. The right ventricular wall measured 14 mm. in thickness and the left ventricular wall 7 mm. The circumference of the pulmonary artery was 58 mm. and that of the aorta 42 mm.

Microscopically the vessels of the second and third order had an intimal thickening which was two or three times the thickness of the media and was formed by loose, cellular connective tissue. In the smallest branches all parts of the walls were thickened, especially the intima, which resulted in marked narrowing and often complete occlusion of the lumens. Fresh thrombi were found here. There was proliferation of connective tissue around the blood vessels.

Other findings included cyanosis of the lips and face, stasis of the abdominal viscera and caseous tuberculosis of the right adrenal gland.

CASE 16 (Ulrich [15]).—In a 31 year old woman, who had suffered hoarseness and amenorrhea for two years, there developed swelling of the feet, ankles and abdomen six months before death. Occasionally blood-streaked sputum occurred.

On physical examination she presented congestive failure with more cyanosis than usual, but with no evidence of moisture at the bases of the lungs. A visible and palpable pulsation was present in the interscapular area (third spinous process), and here a marked systolic bruit could be heard. Roentgen examination revealed a prominent pulmonary bulge and enormously dilated pulmonary arteries at the hilus, the pulsations of which were visible under the fluoroscope. Right axis deviation was present in the electrocardiogram. The hemoglobin concentration and red blood cell count were increased.

At autopsy the pulmonary artery was seen to be extensively dilated, and its branches showed an extreme amount of yellow raised intimal thickening. The right ventricle showed extreme hypertrophy and dilatation.

Microscopically there was seen appreciable intimal thickening in the small arteries, proliferative in character. In many of the small vessels the lumens were almost completely occluded. A marked atheromatous condition was present in the larger vessels.

Other findings included signs of congestive failure.

CASE 17 (Brenner [3]).—In a boy aged 11 dyspnea and dizziness developed. On physical examination the heart was not found to be enlarged. A pulmonary systolic murmur and an accentuated pulmonic second sound were present. The roentgen ray examination revealed a normal-sized heart with a prominent pulmonary artery; the electrocardiogram disclosed right axis deviation.

In the next two years there developed syncopal attacks, with drowsiness, cyanosis, muscular rigidity and incontinence, followed by vomiting. Dyspnea and

15. Ulrich, H. L.: The Clinical Diagnosis of Pulmonary Arteriosclerosis, Ann. Int. Med. **6**:632-644 (Nov.) 1932.

cyanosis continued to increase, and attacks of precordial pain developed. He had at this time a heart slightly enlarged as determined by physical examination, with a harsh systolic pulmonic murmur, an accentuated P wave in lead II and an occasional diastolic pulmonic murmur. The roentgen examination revealed marked prominence and increased pulsation of the pulmonary artery and hilar shadows. The electrocardiogram again revealed right axis deviation. He died suddenly, during an attack of precordial pain.

At necropsy there were noted congestion and edema of the lower lobes of the lungs. The stem and main branches of the pulmonary artery had a thickened wall and a thickened and pitted intima; a few atherosclerotic patches were seen. The heart was enlarged and markedly dilated, with great hypertrophy of the right ventricle. The right auricle was not dilated or hypertrophied.

Microscopically slight sclerosis of the stem of the pulmonary artery and thickening of the media were seen. Many of the small arteries presented intimal proliferation with great narrowing of the lumens. Some had proliferation of the elastica interna; others showed hypertrophy of the media. The lung parenchyma presented no significant changes.

CASE 18 (Mallory [16]).—A boy aged 10 years complained of dyspnea on exertion with cyanosis for two years and swelling of the legs for eight months preceding his admission to the hospital. He was unable to lie flat in bed and had nocturia and emesis.

Physical examination showed dyspnea, cyanosis of the lips and a barrel-shaped chest with bulging of the precordium. Rales were present at the bases of both lungs, and breath tones were diminished to absent. The veins of the neck were enlarged and pulsating. The heart was enlarged to the right and left, and a presystolic gallop rhythm was heard over the entire precordium. The electrocardiogram revealed right axis deviation, an inverted T wave in lead III, high P waves in leads I and II and a depressed ST interval in lead II. The roentgen examination showed the heart enlarged to the right, with increased density at the bases of the lungs.

Death was due to progressive decompensation.

At autopsy the lungs were heavy and less crepitant than normal. A small pulmonary infarct was present. The right ventricle was greatly hypertrophied and dilated. The left and the right auricle were considerably dilated. The left ventricle was normal. Fibrous thickenings almost as thick as the muscle, with focal calcification, were present in the left auricle.

Microscopically an obliterative process was seen in the majority of the smaller vessels, the veins as well as the arteries. There was internal thickening in some of the larger veins (possibly related to the process in the auricle). The alveolar walls were thicker than normal, and dilatation of the lymphatics was seen. A few areas of scarring were present.

CASE 19 (Killingsworth and Gibson [17]).—A boy aged 10 complained of attacks of unconsciousness which came on while playing, preceded by choking and inability to breathe. During these attacks the skin became blue and the extremities cold.

16. Cor Pulmonale, Etiology Unknown, Cabot Case 23511, New England J. Med. **217**:1045-1049 (Dec. 23) 1937.

17. Killingsworth, W. P., and Gibson, S.: Primary Proliferative Pulmonary Arteriolar Sclerosis, Am. J. Dis. Child. **57**:1099-1109 (May) 1939.

The pertinent physical findings included an enlarged heart in gallop rhythm, a thrill and a diastolic murmur at the pulmonary area and a blood pressure of 84 systolic and 72 diastolic; the liver edge was palpable 1½ inches (3.8 cm.) below the costal margin. Roentgen examination disclosed slight cardiac enlargement with extreme prominence of the pulmonary conus. The electrocardiogram revealed right axis deviation. Death was sudden.

At autopsy there were small focal atelectatic areas in the basilar portions of both lungs and dilatation of the pulmonary arterial system. The right ventricle and right auricle were markedly dilated.

Microscopically the pulmonary vessels 1 to 2 cm. in diameter showed moderate proliferation in the intima and slight change in the media. Vessels smaller than 1 cm. in diameter showed marked intimal proliferation, resulting in many instances in complete occlusion.

Comment.—As already stated, the 20 cases the histories of which have just been chronicled probably do not constitute a complete list of those that may qualify for inclusion in the restricted group under discussion. However, it does appear that the majority of the 100 or more cases which are now recorded in the literature under the title of primary pulmonary arteriolar or vascular sclerosis may be excluded, because their records indicate that some pathologic process (pulmonary, pleural, cardiac, etc.) in addition to the pulmonary vascular disease was present which might have been responsible for strain of the right side of the heart. On the other hand, some cases, such as the one reported by Seely,[18] probably should be included, for although "pulmonary emphysema" was mentioned in the anatomic diagnosis, the amount of emphysema indicated by the description of the lungs was so slight as to be practically negligible as a factor in the production of strain of the right ventricle.

An interesting and puzzling group of cases are those in which there is a clinical picture of severe primary cor pulmonale but in which at autopsy there is no evidence of any lesion whatever, either in the pulmonary vessels or elsewhere, to account for the marked hypertrophy of the right side of the heart. Striking examples are case II of Ulrich[15] and some of the cases reported recently by East[19] and by de Navasquez, Forbes and Holling.[20] The latter authors, impressed with the total absence in their cases of a cause for the right-sided heart strain, questioned the significance of the pulmonary vascular lesions in all other cases; they proposed the abandonment of the term "primary pulmonary vascular sclerosis" and suggested in its place the term "idiopathic right ventricular hypertrophy."[21] East[19] preferred the designation of "pulmonary hypertension."

ANALYSIS OF SIGNS AND SYMPTOMS

Both sexes were represented evenly.

The ages varied from 10 to 74, but in only 4 cases were the patients 50 or over, and in 14 cases they were under 40.

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18. Seely, H.: Primary Obliterative Pulmonary Arteriolar Sclerosis, J. A. M. A. **110**:792-794 (March 12) 1938.

19. East, T.: Pulmonary Hypertension, Brit. Heart J. **2**:189-200 (July) 1940.

20. de Navasquez, S.; Forbes, J. R., and Holling, H. E.: Right Ventricular Hypertrophy of Unknown Origin: So-Called Pulmonary Hypertension, Brit. Heart J. **2**:177-188 (July) 1940.

21. Perhaps a better term would be "idiopathic cor pulmonale," which would indicate changes in the right auricle as well as in the right ventricle.

The most important sign, one present in all cases, is the roentgenographic demonstration of enlargement, dilatation or prominence of the pulmonary artery and conus. As a corollary to this, although not so universally constant, is the electrocardiographic demonstration of pronounced right axis deviation, along with other alterations in the auricular and ventricular complexes indicating an extreme degree of cor pulmonale.

Dyspnea was present in 14 of the 20 cases reviewed. Orthopnea was present in 4. Cyanosis of varying degree was noted in 14 and palpitation in 5. Fainting spells were present in 3, pain in the chest or anginal pain in 4, vomiting in 5, dizziness in 5, hemoptysis in 3 and cough in 4. Cardiac murmurs were noted in 7 and thrills in 2. Other symptoms occurring occasionally were headache, anorexia, somnolence, hoarseness, anemia, fever and tightness about the chest.

Congestive failure, affecting the systemic venous system, varying in degree from slight to extreme, occurred in most of the cases; congestion or edema of the lung was comparatively infrequent. Pulmonary atelectasis was noted more often.

Readings of the blood pressure were available in only 4 of the 20 cases. They were: 125 systolic and 95 diastolic; 125 systolic; 90 systolic and 75 diastolic, and 84 systolic and 75 diastolic. The venous pressure was elevated in most of the cases.

Death occurred suddenly in 5 instances.

In 2 of the 20 cases the condition was correctly diagnosed during life.

DIAGNOSIS

An examination of the signs and symptoms just described indicates that they do not differ in any essential respect from those which occur in other types of cor pulmonale secondary to cardiopulmonary disease. The diagnosis therefore depends on the following factors: (1) the demonstration (especially by roentgenographic and electrocardiographic means) of the existence of pronounced strain of the right ventricle *but not of the left*, and (2) the exclusion, by every available means, of all other known causes of right ventricular strain, especially chronic pulmonary disease, mitral stenosis and congenital heart disease. In the presence of clear lung fields and in the absence of murmurs the differential diagnosis is comparatively easy. Unfortunately, in many cases murmurs, and even thrills, develop during the course of the disease, and in some instances the lung fields become obscured, from pressure due to effusion in the pleural and the pericardial sacs, from infarctions, from edema of congestion or from low grade inflammatory processes.

Several authors have stressed the importance of cyanosis in a degree out of proportion to the amount of dyspnea as a sign in favor of primary

pulmonary vascular sclerosis. In cor pulmonale secondary to pulmonary disease dyspnea is more apt to equal or exceed in degree the prevailing cyanosis.

ETIOLOGY AND PATHOGENESIS

Concerning the nature of the pathogenic process affecting the pulmonary vessels nothing definite is known. Probably many variable factors are involved, since great variation is encountered in the character and location of the lesions, as well as in their severity. In some instances the microscopic changes suggest a possible infectious process; in others the changes appear to be degenerative and are similar to those which commonly attack the systemic vessels. Yet notwithstanding this variability of the pulmonary vascular lesions, the anatomic changes of the right ventricle and the resultant clinical manifestations are remarkably uniform in all cases. This circumstance, together with the fact that extensive obstructive disease of the pulmonary vascular bed may occur without any apparent right ventricular strain and without any clinical symptoms, raises the question whether an etiologic relation between the pulmonary arterial disease and the strain of the right side of the heart may be regarded as definitely established.

However, although it may be admitted that such relation cannot be proved for all cases, it can be shown from both experimental and clinical observations that obstructive pulmonary vascular disease may produce severe and fatal strain of the right side of the heart, with the complete clinical picture which characterizes the special group of cases under discussion. Experimentally this syndrome has been repeatedly produced in dogs by graded compression of the pulmonary artery, with uniform results.[22] Clinically, manifestations similar to those seen in severe types of primary pulmonary arteriolar sclerosis with identical anatomic changes in the right cardiac chambers have been observed to develop rapidly from obliteration of the pulmonary vascular bed by metastatic carcinoma.[23] The conclusion therefore appears justified that at least in some of the cases the obliterative pulmonary vascular disease bears a direct etiologic relation to the accompanying changes in the right side of the heart and the resultant clinical manifestations.

The uniform character in almost all cases of the anatomic alterations of the right cardiac chambers suggests that these alterations represent a response to a common factor, possibly pulmonary hypertension. The hypothesis naturally suggests itself that all these cases, whether or not there is associated pulmonary vascular disease, represent primarily a

22. Fineberg, M. H., and Wiggers, C. J.: Compensation and Failure of the Right Ventricle, Am. Heart J. **11**:255-263 (March) 1936.

23. Greenspan, E. B.: Carcinomatous Endarteritis of the Pulmonary Vessels Resulting in Failure of the Right Ventricle, Arch. Int. Med. **54**:625-644 (Oct.) 1934. Brill and Robertson.[3]

physiopathologic response to pulmonary hypertension of unknown origin, perhaps analogous to essential systemic hypertension. The assumption of this hypothesis implies further that such changes in the pulmonary vessels as may be found are merely secondary to the hypertension, that these changes may or may not attain important proportions and that the resultant clinical picture, being dependent chiefly on the pulmonary hypertension, is not significantly affected by the degree of the associated pulmonary vascular damage. This theory receives possible confirmation from the fact that loud, booming pulmonic second sounds and violently pulsating pulmonary arteries as seen under the fluoroscope are observed with equal regularity in those cases in which no pulmonary arteriosclerosis is found, as well as in those in which extensive pulmonary vascular disease is present.

Unfortunately, no clinically satisfactory method for testing the blood pressure of the lesser circuit is as yet available, and until such a method is developed the attractive theory of essential pulmonary hypertension must remain an interesting but unproved speculation.

SUMMARY

A discussion of the literature on primary pulmonary arteriosclerosis is presented with the report of a case recognized during life.

The signs and symptoms are analyzed for a group of 20 cases selected from the literature and including the case now reported.

Principles of diagnosis are suggested.

Theories concerning etiology and pathogenesis are discussed, with especial reference to the possibility of an essential pulmonary hypertension bearing a relation to strain of the right side of the heart analogous to the effect of essential systemic hypertension on the left side of the heart.

RESPONSE OF NORMAL SUBJECTS TO ACUTE BLOOD LOSS

WITH SPECIAL REFERENCE TO THE MECHANISM OF RESTORATION OF BLOOD VOLUME

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Studies on the response of the body to acute blood loss are of both theoretic and practical importance because hemorrhage is a serious complication in many medical and surgical conditions. In man, controlled observations on the effect of hemorrhage on the circulation, the plasma volume, the protein concentration and the cell-plasma ratio are difficult to obtain because the immediate care of the patient requires the complete attention of the physician and because the amount of blood lost is not known. In addition, the underlying disease producing the hemorrhage may alter the response of the body.

Although many investigators have studied the effect of acute blood loss on lower animals, few studies on human subjects have been made under controlled conditions. Keith [1] observed changes in hematocrit reading and blood volume as determined by the dye method after the removal of 800 cc. of blood from a normal man. He found that one hour after removal of the blood the plasma volume had risen above the value obtained before hemorrhage, although the hematocrit reading remained unchanged. Waterfield [2] determined the blood volume by the carbon monoxide method in 2 subjects after the removal of 550 cc. of blood. In 1 case the blood volume determined immediately after hemorrhage was 670 cc. above the prehemorrhage level, while in the other it was 210 cc. lower.

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1. Keith, N. M.: Blood Volume Changes in Wound Shock and Primary Hemorrhage, Medical Research Council, Special Report Series, no. 27, London, His Majesty's Stationery Office, 1919.

2. Waterfield, R. L.: The Effects of Posture on the Circulating Blood Volume, J. Physiol. **72**:110 (June 6) 1931.

Because of lack of evidence on the subject, the effect of acute blood loss on normal subjects under controlled conditions was studied.

METHOD

Six normal professional blood donors who had not given blood during the previous six months served as subjects for the experiments. They were hospitalized for the duration of the study. The morning after their admission the basal plasma volume was determined by the dye method of Gibson and Evans [3] as adapted to the Evelyn microcolorimeter.[4]

The cell-plasma ratio was determined by the hematocrit, with a 1.6 per cent solution of potassium oxalate used to prevent coagulation.[5] The total red cell volume was calculated from the plasma volume and the hematocrit reading. The concentration of hemoglobin was determined by the method of Evelyn [5]; the serum protein concentration, by the falling drop method as described by Kagan.[6] The total circulating protein, in grams, was obtained by multiplying the serum protein concentration, in grams per hundred cubic centimeters, by the plasma volume, in hundreds of cubic centimeters. The samples of blood were taken without stasis. Twenty-four to forty-eight hours later venesection was performed with the subject in the basal state and in a horizontal position. The protein concentration, the hemoglobin concentration, the hematocrit reading and the plasma volume were followed for the next three to four days. In 3 subjects 1,000 cc. of physiologic solution of sodium chloride was given immediately after venesection. All subjects were given 10 to 15 mg. of paredrinol sulfate (α-N-dimethyl-p-hydroxyphenethylamine sulfate) intravenously on the day of venesection to determine whether this drug was effective in raising the arterial pressure in the presence of a diminished blood volume. These results will be reported later. With 1 exception, the plasma volume was not determined for at least four hours after administration of the drug (table). The subjects fasted twelve hours before venesection and continued to fast for twelve hours after venesection. Thereafter they were on the ordinary hospital diet. Water was not restricted at any time.

RESULTS

Changes in Blood Pressure, Pulse Rate and Clinical Condition.—In the 6 subjects studied 760 to 1,220 cc. of blood, or from 15.5 to 19.7 per cent of the blood volume, was removed in six to thirteen minutes. The entire procedure was painless; the subjects could not see the blood,

3. Gibson, J. G., II, and Evans, W. A., Jr.: Clinical Studies of Blood Volume: Clinical Application of Method Employing Azo Dye, "Evans Blue," and Spectrophotometer, J. Clin. Investigation **16**:301 (May) 1937.

4. Gibson, J. G., II, and Evelyn, K. A.: Clinical Studies of Blood Volume: Adaptation of Method to Photoelectric Micro-Colorimeter, J. Clin. Investigation **17**:153 (March) 1938.

5. Evelyn, K. A.: Stabilized Photoelectric Colorimeter with Light Filters, J. Biol. Chem. **115**:63 (Aug.) 1936.

6. Kagan, B. M.: A Simple Method for the Estimation of the Total Protein Content of Plasma and Serum: II. The Estimation of the Total Protein Content of Human Plasma and Serum by Use of the Falling Drop Method, J. Clin. Investigation **17**:373 (July) 1938.

Effect of Venesection on Six Normal Subjects

Date	Time	Hematocrit Reading, Percentage	Hemoglobin, Gm. per 100 Cc.	Total Protein, Gm. per 100 Cc.	Plasma Volume, Cc.	Red Cell Volume, Cc.	Total Blood Volume, Cc.	Theoretic Red Cell Volume, Cc.	Total Circulating Protein, Gm.	Protein Added After Bleeding, Gm.	Procedure
J. C., male, age 33, ht. 176 cm., wt. 80 Kg.											
2/1/40	9:10 a.m.	48.2	.....	....	2,980	2,770	5,750				
2/2/40	9:33 a.m.	48.8	16.25	6.80	.....	.....	.....	.....	203		
	9:39-9:47	....	.....	....	.....	.....	.....	.....	...	..	1,070 cc. of blood removed (plasma 550 cc., cells 520 cc.)
	9:51	48.4	16.05	6.50							
	10:07	47.4	15.80	6.42							
	10:23	46.7	15.40	6.30	2,660	2,340	5,000	2,230	167	4	
	10:27	....	.....	....	.....	.....	.....	.....	...	..	15 mg. paredrinol sulfate i.v.
	11:51	47.1	15.10	6.30							
	4:35 p.m.	44.8	14.80	6.40	2,900	2,560	5,200	2,160	186	28	
2/ 3/40	9:30 a.m.	42.3	13.20	6.22							
2/ 4/40	9:30 a.m.	41.0	12.90								
2/ 5/40	9:15 a.m.	38.6	12.20	6.20	3,300	2,120	5,480	2,130	208	55	
R. C., male, age 35, ht. 174 cm., wt. 61.4 Kg.											
2/ 8/40	9:45 a.m.	46.9	14.6	7.00	2,590	2,280	4,870	.....	...	181	
2/ 9/40	9:26 a.m.	47.5	15.4	7.10							
	9:31-9:39	....	.....	....	.....	.....	.....	.....	...	..	760 cc. of blood removed (plasma 395 cc., cells 365 cc.)
	9:37	46.7	15.3	7.00							
	9:48	45.0	14.9								
	10:07	44.9	14.6	6.60							
	10:27	44.3	14.8	6.51	2,340	1,860	4,200	1,900	152	1	
	10:35	....	.....	....	.....	.....	.....	.....	...	..	10 mg. paredrinol sulfate i.v.
	11:53	44.2	14.9	6.90							
	1:50 p.m.	42.2	13.9	6.80							
	5:20 p.m.	41.3	13.7	6.60	2,530	1,790	4,320	1,860	167	20	
2/10/40	9:45 a.m.	38.2	13.1	6.60							
2/11/40	11:00 a.m.	37.4	.....	6.62							
2/12/40	9:10 a.m.	35.5	11.6	6.44	3,200	1,760	4,960	1,820	206	64	
M. K., male, age 21, ht. 168 cm., wt. 63.2 Kg.											
2/27/40	9:30 a.m.	43.9	.....	6.90	2,840	2,230	5,070	.....	196		
2/28/40	9:23 a.m.	44.5	14.9	7.00							
	9:32-9:40	....	.....	....	.....	.....	.....	.....	...	..	1,000 cc. of blood removed (plasma 540 cc., cells 460 cc.)

	9:50	43.1	14.6	6.80							
	10:06	....	.....	....	.....	.....	.....	.....	...	..	10 mg. paredrinol sulfate i.v.
	10:44	43.0	14.5	6.83							
	11:31	41.8	13.8	6.70	2,500	1,810	4,310	1,760	108	8	
	12:30 p.m.	42.3	13.9	6.70							
	3:10	41.9	13.6	6.83							
	5:25	40.2	13.9	6.83							
2/29/40.....	8:55 a.m.	36.1	12.0	6.60	3,010	1,710	4,720	1,730	199	44	
3/ 1/40.....	9:30 a.m.	34.8	11.6	6.70							
3/ 2/40.....	9:10 a.m.	33.0	11.4	6.60	3,250	1,600	4,850	1,720	215	63	
J. F., male, age 24, ht. 183 cm., wt. 63.8 Kg.											
3/25/40.....	11:05 a.m.	46.0	.....	....	2,870	2,440	5,310				
3/27/40.....	10:23 a.m.	46.7	15.70	7.00	.....	.....	.....	.....	201		
	10:40-10:46	....	.....	....	.....	.....	.....	.....	...	..	960 cc. of blood removed (plasma 490 cc., cells 470 cc.)
	10:50	46.2	15.70	6.90							
	10:50	....	.....	....	.....	.....	.....	.....	...	..	15 mg. paredrinol sulfate i.v.
	11:16	....	15.40	6.83							
	11:23-12:00	....	.....	....	.....	.....	.....	.....	...	..	1,000 cc. of physiologic solution of sodium chloride i.v.
	12:02 p.m.	39.5	13.40	5.80							
	12:33	39.6	13.40	6.00							
	12:57	41.7	13.60	6.30							
	2:20	42.1	14.40	6.42							
	3:20	42.7	14.10	6.42	2,600	1,950	4,550	1,930	167	5	
	5:45	41.0	14.50	6.50							
3/28/40.....	9:00 a.m.	40.0	13.50	6.63							
3/29/40.....	9:45 a.m.	37.4	12.40	6.60							
3/30/40.....	9:13 a.m.	34.1	11.55	6.40	3,370	1,750	5,120	1,900	216	58	
T. W., male, age 24, ht. 173 cm., wt. 70.6 Kg.											
4/13/40.....	9:40 a.m.	45.8	15.9	7.21	3,580	3,020	6,600	.....	258		
4/15/40.....	10:10 a.m.	45.1	16.3	7.20							
	10:18-10:31	....	.....	....	.....	.....	.....	.....	...	..	1,230 cc. of blood removed (plasma 630 cc., cells 600 cc.)
	10:40	44.8	15.9	7.20							
	10:43	....	.....	....	.....	.....	.....	.....	...	..	10 mg. paredrinol sulfate i.v.
	10:55	45.2	16.1	7.30							
	11:01	45.3	15.5	7.20							
	11:04	....	.....	....	.....	.....	.....	.....	...	..	1,000 cc. of physiologic solution of sodium chloride i.v. started
	11:21	40.4	14.3	6.60							
	11:42	....	.....	....	.....	.....	.....	.....	...	..	Injection of saline solution completed

Effect of Venesection on Six Normal Subjects—Continued

Date	Time	Hematocrit Reading, Percentage	Hemoglobin, Gm. per 100 Cc.	Total Protein, Gm. per 100 Cc.	Plasma Volume, Cc.	Red Cell Volume, Cc.	Total Blood Volume, Cc.	Theoretic Red Cell Volume, Cc.	Total Circulating Protein, Gm.	Protein Added After Bleeding, Gm.	Procedure
T. W.—Continued											
	11:45	39.4	.....	6.07							
	12:30 p.m.	39.4	13.7	6.52							
	1:20	41.3	13.9	....							
	2:30	41.1	14.0	6.60							
	4:40	40.5	14.0	6.62	3,210	2,210	5,420	2,370	213	5	
	9:00	40.1	13.7	6.62							
4/16/40.....	10:02 a.m.	37.9	12.5	6.44	3,545	2,165	5,710	2,350	228	24	
	4:30 p.m.	35.4									
4/17/40.....	9:43 a.m.	34.2	11.5	6.23	3,940	2,000	6,000	2,320	245	44	
4/18/40.....	11:15 a.m.	35.2	11.7	6.62							
4/19/40.....	9:21 a.m.	33.2	11.4	6.50	4,130	2,050	6,180	2,300	268	70	
A. B., male, age 38, ht. 160 cm., wt. 58.6 Kg.											
4/ 1/40.....	11:00 a.m.	47.0	.....	....	2,580	2,280	4,860				
4/ 3/40.....	9:50 a.m.	47.0	14.9	6.70	.....	.....	.....	.....	173		
	9:59-10:07	....	.....	....	.....	.....	.....	.....	...	..	800 cc. of blood removed (plasma 410 cc., cells 390 cc.)
	10:11	....	.....	....	.....	.....	.....	.....	...	..	10 mg. paredrinol sulfate i.v.
	10:27	45.0	14.6	6.42							
	10:34	....	.....	....	.....	.....	.....	.....	...	..	1,000 cc. physiologic solution of sodium chloride i.v. started
	10:47	41.4	13.2	5.90							
	10:59	39.4	12.7	5.60							
	11:10	....	.....	....	.....	.....	.....	.....	...	..	Injection of saline solution completed
	11:12	37.6	12.3	5.50							
	11:37	39.2	12.7	5.70							
	12:22 p.m.	40.3	13.3	5.90							
	12:49	39.2	13.4	5.84							
	2:05	38.0	12.5	5.84							
	3:37	37.4	12.0	5.70	2,890	1,730	4,620	1,840	164	21	
4/ 4/40.....	9:15 a.m.	38.5	12.7	6.60							
4/ 5/40.....	9:15 a.m.	35.8	11.7	6.30							
4/ 6/40.....	9:15 a.m.	34.2	10.9	6.20	3,130	1,620	4,750	1,810	194	51	

and their attention during venesection was distracted by conversation. Circulatory collapse developed in 5 subjects; the sixth had no symptoms.

None of the subjects complained of any symptoms until near the end of venesection, though moderate pallor, cool hands and slight sweating of the forehead appeared. The onset of collapse was sudden, occurring in 2 subjects while the blood was being taken and in 3 subjects from one to four minutes after venesection was completed. In 4 subjects the arterial pressure and the heart rate were carefully followed. Before the onset of collapse there was only a slight fall in the systolic pressure (average 11 mm. of mercury), while the diastolic pressure remained unchanged; the heart rate increased 14 to 30 beats above the basal level. With the onset of collapse both the systolic and the diastolic pressure fell precipitously, and the heart rate became strikingly slow, ranging between 36 and 40 beats per minute. The subjects complained of weakness, nausea, a sensation of weight on the epigastrium and blurred vision. An ashen gray pallor developed, and they retched, perspired profusely and responded slowly, if at all, to commands. One subject became unconscious.

The subjects were placed in the Trendelenburg position when collapse developed. In the 2 subjects with collapse who received no medication, the heart rate remained slow and the systolic pressure below 100 mm. of mercury for thirty minutes. During the next twelve hours they were pale, but their circulation appeared adequate as long as they were recumbent. On standing up, however, they fainted. The other subjects were not allowed out of bed for twenty-four hours after venesection.

Changes in Plasma Volume Following Venesection.—Immediately after hemorrhage there was a sharp drop in plasma volume (table; fig. 1). The plasma volume then gradually increased, until at the end of three to four days it was greater than the original plasma volume by an amount approximately equal to the volume of red blood cells removed. In the 3 cases in which physiologic solution of sodium chloride was not given intravenously determinations of plasma volume were performed thirty-six to one hundred and eleven minutes after hemorrhage. During this brief period the plasma volume increased only 145 to 230 cc., although in these 3 cases 760 to 1,070 cc. of blood had been removed. In none of them, therefore, was there a sudden large increase in plasma volume immediately following hemorrhage. Figure 1 shows the changes in plasma volume following hemorrhage over a period of three days in subject M. K.

Relation of Increase in Plasma Volume to Changes in Serum Protein Concentration.—Immediately after the hemorrhage the total circulating protein was diminished by approximately the amount of protein

removed during venesection. In the first two hours after bleeding the increase in plasma volume was accompanied by a decrease in serum protein concentration and by only a slight increase in total circulating protein. In the 3 cases in which the plasma volume was determined within two hours after hemorrhage the average addition of protein to the plasma was only 5 Gm. This initial increase in plasma volume, therefore, was the result of the addition of a protein-poor fluid to the blood stream. In the 3 subjects who did not receive physiologic solution of sodium chloride this initial period of dilution was completed in less

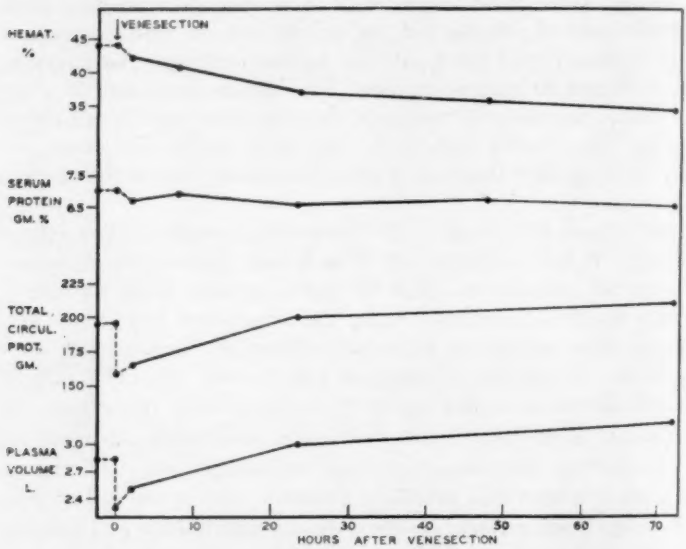

Fig. 1.—Effect of removal of 1,000 cc. of blood (540 cc. of plasma and 460 cc. of red cells) on plasma volume, hematocrit reading, serum protein concentration and total circulating protein in subject M. K.

than two hours. Thereafter, the concentration of the serum protein either did not change or increased slightly (fig. 1). This means that after the initial period of dilution the increase in plasma volume was accompanied by a simultaneous increase in total circulating protein. As protein and fluid were added to the blood at the same time, the protein concentration did not fall as the plasma volume increased.

In 3 cases 1,000 cc. of physiologic solution of sodium chloride was administered intravenously after venesection to determine whether the fluid would be retained in the blood stream. In 2 (J. F. and T. W.) the results were similar. During and after the administration of physio-

logic solution of sodium chloride there was a sharp drop in protein concentration, although never to the level one would expect if all of the solution had been retained within the vascular system. There was a corresponding drop in hematocrit readings (fig. 2). During the three hours after the saline solution was injected the serum protein concentration and the hematocrit reading rose, an indication that fluid was leaving the blood stream. After this period the serum protein concentration remained approximately constant while the hematocrit reading fell, showing that both fluid and protein were being added to the blood stream.

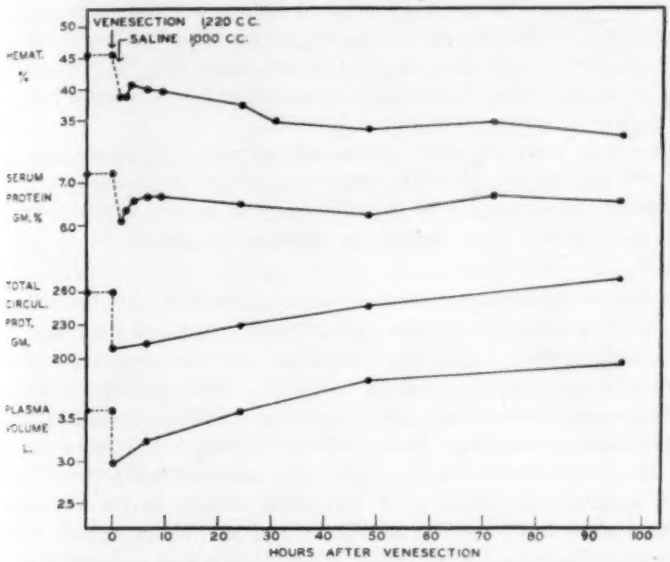

Fig. 2.—Effect of removal of 1,220 cc. of blood (620 cc. of plasma and 600 cc. of red cells) on plasma volume, hematocrit reading, serum protein concentration and total circulating protein in subject J. W. One thousand cubic centimeters of physiologic solution of sodium chloride was given intravenously thirty-three minutes after completion of venesection.

Values for plasma volume determined in these cases three and one-third and five hours, respectively, after administration of physiologic solution of sodium chloride were still 270 and 370 cc., respectively, lower than the prehemorrhage level. In the third case (A. B.) in which such a solution was administered, the dilution lasted much longer. Five hours after hemorrhage the plasma volume was higher than the original prehemorrhage value, and the lowered serum protein concentration showed that considerable dilution was still present.

A study of the qualitative changes in the various plasma proteins was made by Luetscher, using the electrophoretic method.[7] In 3 cases he found no difference in the relative proportion of the albumin and the various globulin fractions in samples of blood taken before hemorrhage and in those taken three days after hemorrhage.

Changes in the Hematocrit Reading.—In those cases in which physiologic solution of sodium chloride was not administered the hematocrit reading gradually fell after hemorrhage. The decrease in hematocrit value paralleled the increase in plasma volume and proved a useful guide in estimating the rate at which the plasma volume was increasing. If the difference between the original hematocrit reading and that made seventy-two hours after venesection is taken as 100 per cent, it is found that 14 to 36 per cent of this drop occurred in two hours, 36 to 50 per cent in eight hours and 63 to 77 per cent in twenty-four hours. Figure 1 shows the decline in hematocrit values in 1 case.

In those cases in which physiologic solution of sodium chloride was given after the bleeding, there was always an immediate drop in hematocrit values due to dilution of blood by the saline solution. This was followed by an increase in values as the solution left the blood stream (fig. 2).

Changes in Red Cell Volume.—At varying periods after hemorrhage the red cell volume was estimated from the plasma volume and the hematocrit reading. This was compared with the predicted red cell volume, which was calculated by subtracting from the red cell volume as determined before bleeding the volume of red cells removed by venesection and by sampling. The results are shown in the table. In the 3 cases in which the blood volume was measured within two hours after hemorrhage, before there was much change in the hematocrit value, the predicted and the determined red cell volume agreed closely (average difference, 1.9 per cent). After dilution had occurred and the hematocrit level had fallen, the predicted and the determined red cell volume no longer agreed. The determined red cell volume was lower than the predicted red cell volume in 5 subjects. In the sixth they were the same. The difference in any 1 case was too small to be significant in itself, but since the discrepancies were always in the same direction, that trend was believed to be significant. Likewise, the red cell volume determined shortly after hemorrhage was always 5 to 12 per cent higher than the red cell volume determined three days later, although only a small amount of blood for samples had been removed in the interim. Similar results have been obtained in bleeding experiments on

7. Luetscher, J. A., Jr.: Electrophoretic Analysis of Plasma and Urinary Proteins, J. Clin. Investigation **19**:313 (March) 1940.

splenectomized dogs.[8] It appears that the total red cell volume cannot be accurately calculated from the plasma volume and the hematocrit reading because, as suggested by Smith, Arnold and Whipple,[9] the cell plasma ratio in large and in small blood vessels is different. This problem will be discussed in detail in a later paper.

COMMENT

These experiments show that if 15 to 20 per cent of the normal blood volume (as determined by the dye method [2]) is rapidly removed from the body circulatory collapse will usually occur. It has been demonstrated previously that an average of 15 per cent of the blood circulating in the head and trunk can be pooled in the extremities by venous tourniquets and that this pooling will produce collapse in some normal subjects.[10] In the experiments with venesection and with tourniquets the blood was removed rapidly. Probably more blood could be removed without producing symptoms if it was done slowly. In spite of the precautions taken, psychic and reflex factors undoubtedly played some part in the onset of the collapse. It is possible that if the experiments had been repeated several times on the same subject more blood could have been removed before collapse occurred.

The onset of the collapse was sudden. Until it occurred the subject had no complaints. In 3 subjects, collapse developed from one to four minutes after venesection was completed. The compensatory mechanism appeared to break down suddenly, even though no more blood was being removed and the position of the subject had not been changed. Before the onset of collapse the heart rate increased moderately, presumably because of the effect of the fall in systolic pressure on the carotid sinus and on other pressor reflexes. At the height of collapse the heart rate became extremely slow. A similar slow heart rate has been noted in certain types of clinical shock, in vasovagal syncope and in advanced stages of collapse induced by sodium nitrite. As pointed out by Weiss, Wilkins and Haynes,[11] subjects at the height of collapse induced by

8. Stead, E. A., Jr., and Ebert, R. V.: Relationship of the Plasma Volume and the Cell Plasma Ratio to the Total Red Cell Volume, Am. J. Physiol. **132**:411 (March) 1941.

9. Smith, H. P.; Arnold, H. R., and Whipple, G. H.: Blood Volume Studies: VII. Comparative Values of Welcker, Carbon Monoxide and Dye Methods for Blood Volume Determinations; Accurate Estimation of Absolute Blood Volume, Am. J. Physiol. **56**:336 (June) 1921.

10. Ebert, R. V., and Stead, E. A., Jr.: The Effect of the Application of Tourniquets on the Hemodynamics of the Circulation, J. Clin. Investigation **19**:561 (July) 1940.

11. Weiss, S.; Wilkins, R. W., and Haynes, F. W.: The Nature of Circulatory Collapse Induce by Sodium Nitrite, J. Clin. Investigation **16**:73 (Jan.) 1937.

sodium nitrite show signs of overactivity of both the sympathetic and the parasympathetic nervous system. It is not known whether ischemia stimulates the parasympathetic centers in the central nervous system directly or reflexly.

The decrease in blood volume by hemorrhage is apparently compensated in two ways: (1) by vasoconstriction and (2) by addition of fluid to the blood stream. The vasoconstriction is shown by pallor, cooling of the extremities and narrowing of the pulse pressure. The addition of fluid to the blood stream is demonstrated by the gradual increase in blood volume. This is accounted for entirely by the increased plasma volume, and there are no demonstrable reserves of red cells which are added to the blood stream in this type of emergency. In the first two hours after venesection the plasma volume is increased by fluid poor in protein. This causes the serum protein concentration to fall. Thereafter, fluid and protein are added to the blood stream at the same time, so that, though the plasma volume continues to increase, the protein concentration falls no farther.

This initial fall in the plasma protein concentration immediately after severe hemorrhage is a well recognized phenomenon. It has been suggested that fluid is added to the blood stream immediately after hemorrhage because of the decreased capillary pressure, which allows the osmotic pressure of the proteins to draw water into the blood stream.[12] The slow increase in plasma volume is not the result of the lack of fluid in the body with which to dilute the blood, because when physiologic solution of sodium chloride is given intravenously the dilution is not maintained. In these experiments it appears that after the initial period of dilution the size of the plasma volume is determined by the quantity of circulating protein. Therefore, a large increase in plasma volume is not maintained until the amount of circulating protein has been increased.

It is established that in cases of surgical shock and of profuse hemorrhage with marked fall in blood pressure physiologic solution of sodium chloride is ineffective in treatment and that only the administration of whole blood or of plasma will produce a lasting rise in blood pressure. Apparently the diminished blood volume can be increased to only a limited degree of the addition of protein-free fluid. Beyond this point it is necessary to add a substance which increases the colloid osmotic pressure of the blood in order to increase the blood volume further. In patients with low plasma protein due to the nephrotic syndrome [13] or to

12. Adolph, E. F.; Gerbasi, M. J., and Lepore, J. J.: The Rate of Entrance of Fluid into Blood in Hemorrhage, Am. J. Physiol. **104**:502 (May) 1933.

13. Harris, A. W., and Gibson, J. G., II: Clinical Studies of the Blood Volume: VII. Changes in Blood Volume in Bright's Disease With or Without Edema, Renal Insufficiency, or Congestive Heart Failure, and in Hypertension, J. Clin. Investigation **18**:527 (Sept.) 1939.

nutritional deficiency [14] the blood volume is low, and with an increase in plasma protein there is an increase in blood volume. In these chronic conditions the amount of total circulating protein is one of the most important factors regulating the blood volume.

Large amounts of protein are not added to the blood stream immediately after hemorrhage, but there is a steady addition of protein for two to three days after venesection. About one fourth of the protein present seventy-two hours after hemorrhage was protein which had entered the blood stream since venesection. The proportions of the albumin and various globulins composing the plasma protein had not changed, indicating that the decrease in blood volume and serum protein caused by hemorrhage had served as a physiologic stimulus for the formation of normal serum protein. The fact that only small amounts of protein were added during the first two hours after venesection shows that the protein is not stored in plasma depots which can be readily emptied into the general circulation, but either that it is stored as prepared protein outside the circulation or that the materials to make the protein are readily available.

Extensive studies on the rate of regeneration of plasma proteins after plasmapheresis have been made on dogs.[15] Immediately after removal of the protein there is no sudden large addition of protein to the blood stream, but a slow, steady regeneration over a period of days, which occurs even if the dog is fasting or is on a protein-poor diet, although it is more rapid on a meat diet. It has been found that if dogs are kept on a protein-deficient diet and subjected repeatedly to plasmapheresis, the plasma proteins are produced more rapidly during the first two to four weeks than later. The excess protein regenerated during this period has been called the protein reserve, and is probably composed chiefly of materials necessary to make the plasma proteins rather than of complete plasma proteins which can enter the blood stream immediately.

The hematocrit readings accurately reflected the direction of the changes in plasma volume in these experiments. An increase in plasma volume caused the reading to fall, and a decrease caused it to rise. After the first two hours the change in plasma volume was much more accurately reflected by the hematocrit value than by the protein concen-

14. Chang, H. C.: Plasma Protein and Blood Volume, Proc. Soc. Exper. Biol. & Med. **29**:829 (April) 1932.

15. Kerr, W. J.; Hurwitz, S. H., and Whipple, G. H.: Regeneration of Blood Serum Proteins: I. Influence of Fasting upon Curve of Protein Regeneration Following Plasma Depletion, Am. J. Physiol. **47**:356 (Dec.) 1918. Smith, H. P.; Belt, A. E., and Whipple, G. H.: Rapid Blood Plasma Protein Depletion and Curve of Regeneration, ibid. **52**:54 (May) 1920. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production, and Utilization, Physiol. Rev. **20**:194 (April) 1940.

tration. The continued increase in plasma volume was not shown by decreased protein concentration because protein was constantly being added to the blood stream, but it was shown by a steady fall in the hematocrit reading because no demonstrable number of red cells were added to the blood stream during the first three days after hemorrhage.

SUMMARY AND CONCLUSIONS

1. Seven hundred and sixty to 1,220 cc. of blood (15.5 to 19.7 per cent of the total blood volume as determined by the plasma volume and the hematocrit reading) was removed from 6 normal subjects in six to thirteen minutes. In 5 of the 6 subjects there developed collapse characterized by weakness, nausea, blurred vision, pallor, sweating and fall in arterial pressure. Before the onset of collapse the heart rate increased from 14 to 30 beats per minute. At the height of collapse the heart rate became slow, ranging between 36 to 40 beats per minute.

2. The plasma volume began to increase immediately after hemorrhage and continued to increase for the next forty-eight to seventy-two hours. At the end of seventy-two hours it was approximately equal to the plasma volume before hemorrhage plus the volume of red cells removed.

3. During the first two hours after venesection the plasma volume was increased by protein-poor fluid, so that the serum protein concentration decreased. Thereafter, fluid and protein were added to the plasma at the same time, and the serum protein concentration remained unchanged, though the total circulating protein increased.

4. At the end of seventy-two hours approximately one fourth of the plasma protein was protein which had been added to the plasma after venesection. Loss of blood acted as a physiologic stimulus for the production of normal protein, and the addition of the new protein did not change the proportions of the albumin and the various globulin fractions.

5. When physiologic solution of sodium chloride was given intravenously immediately after hemorrhage, it was not retained in the blood stream in sufficient quantity to restore the plasma volume to normal.

6. After hemorrhage the blood volume was not restored to normal until new plasma protein had been added to the circulation.

7. Hematocrit readings in these experiments accurately reflected the direction of a change in plasma volume.

CLINICAL LIPOID NEPHROSIS

WITH SPECIAL REFERENCE TO ITS TRANSFORMATION INTO CLINICAL AND PATHOLOGIC CHRONIC GLOMERULONEPHRITIS

GEORGE G. GILBERT, M.D.
DURHAM, N. C.

The purpose of this paper is to present a case of clinical lipoid nephrosis which was studied over a period of four years and finally at autopsy. Nephritis with associated uremia developed terminally, and autopsy revealed the anatomic changes characteristic of chronic glomerulonephritis.

A brief statement regarding the controversies relating to the nature of lipoid nephrosis may be presented to clarify the issues involved in this case.

One group of workers [1] has expressed the belief that lipoid nephrosis is a separate clinical and pathologic entity distinct from chronic glomerulonephritis. Many of this group contended that patients with "pure" lipoid nephrosis will either recover from this disease or die of an intercurrent infection. They also have stated that the diagnosis of lipoid nephrosis is excluded even by the infrequent finding of a few red cells in the urine, slight elevations of blood pressure or a slight rise in blood nonprotein nitrogen. The other group [2] has expressed the opinion that lipoid nephrosis represents simply a stage in the development of that pathologic process which ends in clinical and anatomic chronic glomerulonephritis. Findings in the case reported here constitute good evidence in support of the main thesis of the second group.

From the Department of Pathology, Duke University School of Medicine.

1. Murphy, F. D.; Warfield, L. M.; Grill, J., and Annis, F. R.: Lipoid Nephrosis, Arch. Int. Med. **62**:355 (Sept.) 1938. Aldrich, C. A.: Lipoid Nephrosis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 3, chap. 28, p. 21. Bell, E. T.: Lipoid Nephrosis, Am. J. Path. **5**:587 (Nov.) 1929. Fahr, G.: Lipoid Nephrosis, Am. J. M. Sc. **194**:449 (Oct.) 1937.

2. Blackman, S.: On the Pathogenesis of Lipoid Nephrosis and Progressive Glomerulonephritis, Bull. Johns Hopkins Hosp. **57**:70 (Aug.) 1935. Bennett, T. I.; Dodds, E. C., and Robertson, J. D.: The Conception of "Nephrosis," Quart. J. Med. **24**:239 (Jan.) 1931. Christian, H. A.: Nephrosis: A Critique, J. A. M. A. **93**:23 (July 6) 1929. Mason, E. H.: The Life History of a Case of Nephrosis, Internat. Clin. **1**:163 (March) 1926.

REPORT OF A CASE

Clinical Summary.—(This summary was furnished by Dr. R. Charman Carroll, of the Duke Hospital department of pediatrics.) A 5 year old white girl was admitted to Duke Hospital three and one-half years before death, with the complaint of edema of the abdomen and legs. With rest in bed this condition had

Laboratory Data

				Blood Chemistry				
Admission	Weight, Kg.	Blood Pressure, Mm. of Hg.	Urine, Specific Gravity	Non-protein Nitrogen, Mg./100 Cc.	Total Protein, Mg./100 Cc.	Albumin/Globulin	Cholesterol, Mg./100 Cc.	Treatment *
1†	24.6	138/100	1.032	32	4.20	1/3	397	Acacia (3)
	15.9	.....	1.030	30	5.00	4/5	395	Plasma (2)
2†	19.6	94/ 60	q.n.s.	25	3.00	...	...	Serum (2)
	16.1	.....	q.n.s.	16	4.20	2/5	...	Whole blood (4)
3‡	20.7	.....	1.008	25	4.10	1/2	...	Magnesium sulfate (4)
	20.4	.....	1.030	..	....	...	...	Theobromine with sodium salicylate (3)
4	20.6	120/ 74	.....	27	4.30	3/5	...	Thyroid (5)
5	20.3	120/ 75	1.025	23	....	...	...	Ammonium chloride (3)
	20.0	.....	.....	..	....	...	...	Ammonium nitrate (1)
6	24.7	108/ 78	1.030	28	3.71	3.20	...	Potassium nitrate (1)
	21.8	.....	1.025	..	2.61	1/5	182	Dextrose (3)
7	24.8	100/ 74	1.018	17	2.70	1/5	...	Sucrose (1)
	23.4	.....	1.030	..	....	...	...	Urea (3)
8	22.7	102/ 78	1.026	38	2.80	1/4	...	Pitressin (1)
	22.6	.....	.....	..	....	...	...	Liver extract (1)
9	24.7	120/ 90	1.022	15	3.00	1/4	880	Quinine hydrochloride (1)
	21.7	.....	1.020	20	....	...	...	Amino acids (1)
10	24.4	.....	1.025	39	....	...	1,005	Paracentesis (7)
	20.9	.....	1.030	33	3.64	...	900	Sulfanilamide (1)
11	25.5	120/ 80	1.020	58	3.70	...	1,140	Sulfanilamide (2)
	20.2	.....	1.015	51	....	...	872	
12†‡	20.2	.....	1.025	56	4.10	1/5	...	
	18.8	.....	1.017	33	....	...	...	
13	25.8	156/130	1.014	342	....	...	356	

* A number in brackets indicates the number of times a type of therapy was given.
† Occasional red blood cells were found in the urine.
‡ The content of albumin in three twenty-four hour samples of urine was 3.4, 6.0 and 8.0 Gm., respectively, per hundred cubic centimeters.

cleared, but had returned and progressed to generalization when the patient again became ambulatory. No hematuria had been noted.

On the patient's first admission to the hospital, six months after appearance of the initial symptoms, the temperature was 38.5 C. (101.3 F.), the pulse rate 135, the respiratory rate 28 and the blood pressure 138 systolic and 100 diastolic. The child appeared acutely ill with extensive generalized pitting edema, ascites and pulmonary congestion. The tonsils were enlarged and infected. The hemoglobin concentration was 85 per cent, the red cell count 4,500,000 and the white cell count 16,700. The urine gave a 4 plus reaction for albumin, contained many white blood

cells and occasional red blood cells and hyaline casts and had a specific gravity of 1.032. The Wassermann reaction of the blood was negative (see table for other laboratory data).

During the next four months, the patient did not improve in spite of numerous types of therapy (see table), which included administration of 86 Gm. of acacia in doses of 15 to 23 Gm. Orbital abscesses and estivoautumnal malaria occurred during this period. In the fourth month of hospitalization, the urinary output increased rapidly and the edema receded without relation to specific therapy.

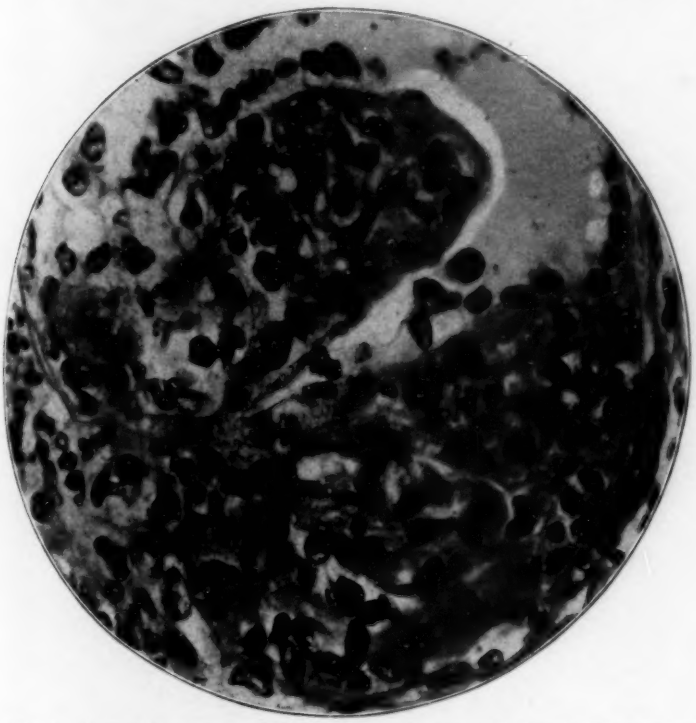

Fig. 1.—A typical glomerulus with widespread acute and chronic inflammatory reaction.

Throughout the period of observation urinalysis gave a 3 to 4 plus reaction for albumin, showed 0 to 8 red blood cells per high power field and few to many white blood cells and casts and had a specific gravity of 1.029 to 1.032.

Within the three years preceding death the child was admitted to the hospital twelve more times. One admission was for a tonsillectomy and adenoidectomy. The others, like the first, were for nephrotic attacks, lasting from two weeks to five months, and were usually associated with infections of the upper respiratory tract. Laboratory findings were similar to those of the first period of hospitalization, except that red blood cells were found in the urine in the course of only two

of the twelve periods (see table). Results of the phenosulfonphthalein excretion test and the basal metabolic rate were within normal limits.

The thirteenth and last admission occurred approximately four years after the initial attack of the child's long illness. At this time the complaint was generalized edema of one week's duration, cough, vomiting and fever of twenty-four hours' duration. The temperature was 37.9 C. (100.2 F.), pulse rate 120, respiratory rate 24 and blood pressure 155 systolic and 130 diastolic. The patient was acutely ill, lethargic and dyspneic. The complexion was waxy, and there was marked gen-

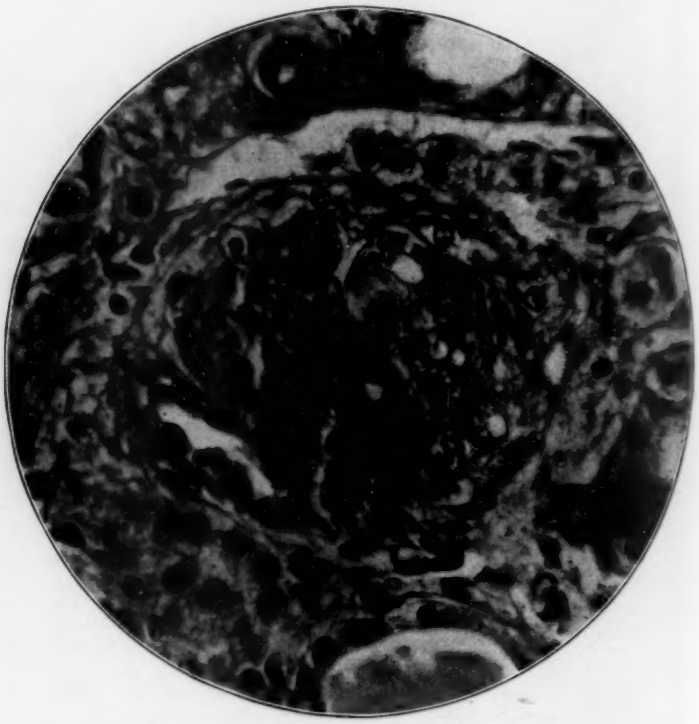

Fig. 2.—A completely hyalinized glomerulus.

eralized pitting edema with ascites and pulmonary congestion. The heart was enlarged in all diameters; the rate was rapid, but no murmurs were heard. The electrocardiogram indicated myocardial injury. The hemoglobin concentration was 45 per cent, the red cell count 2,770,000, and the white cell count 12,040. The carbon dioxide–combining power was 32 volumes per cent and the nonprotein nitrogen content 342 mg. per hundred cubic centimeters. Therapy consisted of administration of a molar solution of sodium lactate by mouth, small blood transfusions, intravenous injection of a 25 per cent solution of sucrose and paracenteses (cultures of the fluid were negative). The day following admission a friction rub was heard over the entire precordium. Edema increased, and the urinary output remained below 300 cc. per day. The child died suddenly one week after admission.

Clinically, this patient was thought to have nephrosis the diagnosis having been based on the following essential findings: continuous albuminuria with red blood cells observed infrequently (during only three of the thirteen periods of hospitalization); insidious onset of the illness without previous history of infection; normal level of nonprotein nitrogen until the last admission; pronounced edema, which recurred ten times; normal blood pressure, except on the first and last admissions; increased blood cholesterol, and low total serum proteins, with a reversal of the albumin/globulin ratio. However, terminally the clinical picture was no longer

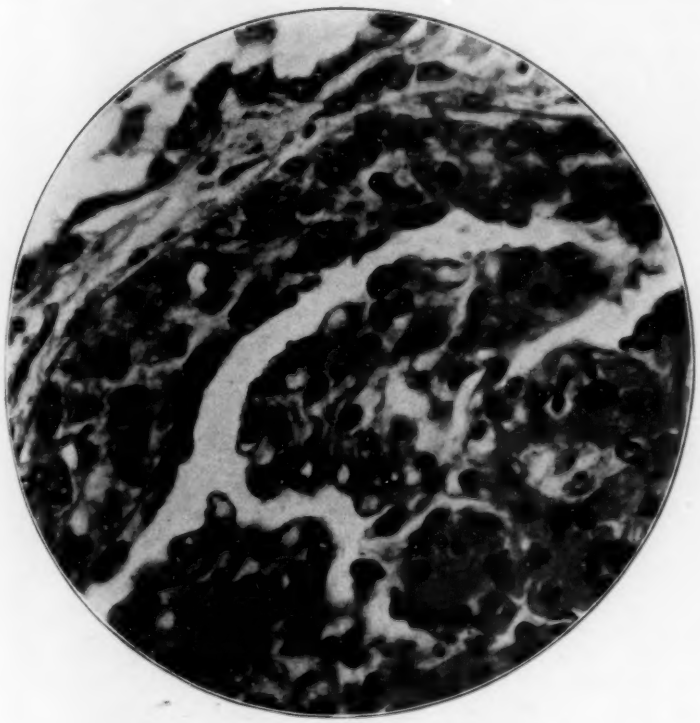

Fig. 3.—A glomerulus with a typical crescent.

that of nephrosis but that of typical glomerulonephritis with associated uremia (see table for data).

Autopsy Protocol.—The diagnoses made at autopsy included: chronic glomerulonephritis; cardiac dilatation; anasarca; fibrinous pericarditis (uremic); prominent fat deposits in the aortic and the mitral valves and in the intima of the coronary arteries and the aorta; submucosal edema of the colon and the bladder and storage of acacia in the liver.

Extreme anasarca was present. The abdominal cavity contained 880 cc. of a frothy cloudy fluid in which there were no bacteria. The heart weighed 100 Gm., which was within normal limits for a child of this age (8½ years) and height

(115 cm.). The cavities were considerably dilated. Fibrinous pericarditis was present. There were extremely fatty atheromatous plaques in the aortic and the mitral valves, in the coronary arteries and throughout the entire length of the aorta, where they were concentrated in the distal portion, there giving rise to considerable narrowing of the lumen. Microscopically these plaques appeared similar to those seen in the aortas of adults. Under the polarizing microscope, both in a section stained for fat (with scarlet red) and in an unstained frozen section, doubly refractile crystals of cholesterol esters were observed. Some of the stained fat

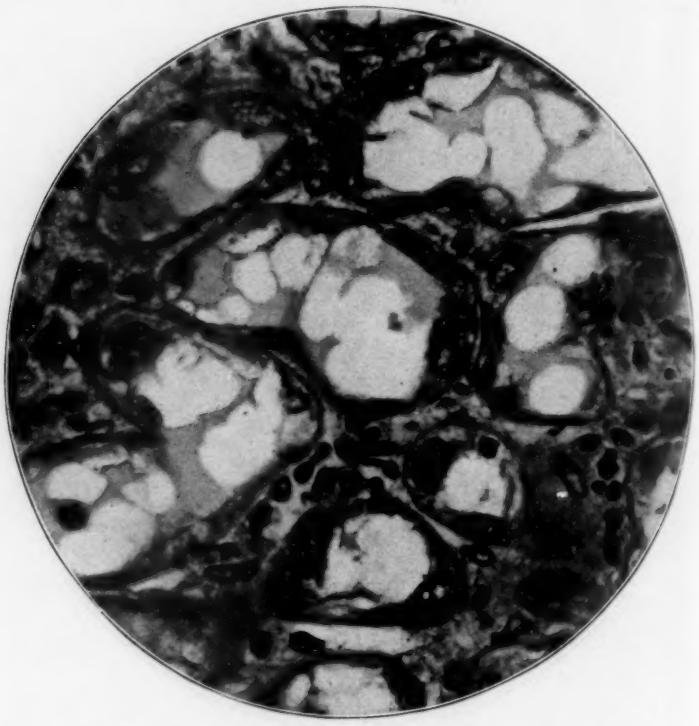

Fig. 4.—Dilated convoluted tubules containing coagulated protein and lined with small flat cells and large regenerating cells.

was not doubly refractile, and therefore it was recognized as neutral fat. The use of nile blue sulfate stain confirmed this differentiation. Both lungs contained numerous small areas of atelectasis. The liver was large, weighing 1,070 Gm. The cut surface was swollen and puffy, with conspicuous lobules. Microscopically it appeared to contain acacia. This was confirmed by comparison with livers known to contain acacia and by chemical analysis. This aspect of the case, storage of acacia in the liver, is being reported separately. The submucosa of both the colon and the urinary bladder was edematous.

The weight of each kidney, 100 gm., was within normal limits considering the age and height of the patient. There was no variation in general appearance between

the two kidneys. The surfaces were pitted by fine shallow scars and spotted with many small hemorrhagic flecks. The cortex was narrow and brownish gray. Most of the cortical striae were irregular and distorted. The glomeruli exhibited a homogeneous eosinophilic supporting structure due to fibrosis, fibrinous exudate and hyaline alteration of the greatly thickened basement membrane (figs. 1 and 2). Many of the dilated capsular spaces were filled with coagulated protein. Numerous typical crescents were present (fig. 3). Glomeruli showing capsular adhesions covered with epithelium were conspicuous. Some of the glomeruli were the seat of extreme fat deposits. Only a small portion of the fat was cholesterol or its esters, as determined by examination with the polarizing microscope. Most of the convoluted tubules were dilated and contained coagulated protein (fig. 4). Some contained cellular casts and, in some instances, red blood cells. The tubular epithelium was flattened, and the cells seemed to be decreased in number. Interspersed among the flattened cells were large oval cells with vesicular nuclei thought to represent regenerating tubular epithelium. Similar changes were noted in the collecting tubules. Fat was contained in only a few of the tubular cells, and it was not anisotropic. The arterioles showed no changes. The interstitial tissue was infiltrated with lymphocytes and fibroblasts. The pelves showed no change.

COMMENT

Anasarca, albumin in the urine, lowered serum proteins, reversal of the albumin/globulin ratio, high blood cholesterol, normal blood pressure, normal nonprotein nitrogen and infrequent occurrence to complete absence of red blood cells in the urine were all exhibited in this case. The changes mentioned represent the usual criteria for the diagnosis of lipoid nephrosis. However, many authors would not consider the condition in this case a "pure" example, because of the red cells noted in the urine and the slightly elevated blood pressure present at the time of the patient's first admission to the hospital. On the contrary, my associates and I are inclined to agree with Blackman,[3] who has expressed the opinion that there may be examples of lipoid nephrosis which are "pure" but in which there are an occasional rise in blood pressure and a few red cells in the urine. If the patient had had glomerulonephritis for four years we should have expected to find small contracted kidneys. Furthermore, the fact that the glomeruli showed both old and fresh lesions suggested that the process had been in progress some time before the clinical evidence of nephritis developed. Thus, it is obvious that there is only indirect pathologic evidence that the patient once had lipoid nephrosis. Nevertheless, these pathologic anatomic observations, coupled with the long duration of the disease, the thorough and continuous clinical observation and the laboratory data, have led us to believe that we are dealing with a case of lipoid nephrosis which was terminated not by recovery or by fatal intercurrent infection, as this disease so often is, but by the progressive devel-

3. Blackman, S.: Pneumococcal Lipoid Nephrosis and the Relation Between Nephrosis and Nephritis, Bull. Johns Hopkins Hosp. **55**:1 (July) 1934.

opment of its basic pathologic process to the point that its final state was identical clinically and anatomically with chronic glomerulonephritis.

SUMMARY

A case is presented in which were exhibited all of the typical features of lipoid nephrosis. The patient, a white child, was followed for four years, during which time careful clinical studies were facilitated by her being admitted to the hospital thirteen times. On the final admission it was discovered that the clinical picture had changed to such an extent that the diagnosis of lipoid nephrosis was no longer tenable, since all of the typical signs and symptoms of chronic glomerulonephritis had developed. The terminal clinical diagnosis of chronic glomerulonephritis was confirmed by autopsy, which revealed the typical anatomic lesions of chronic glomerulonephritis.

The observations recorded in this case appear to support the thesis that lipoid nephrosis and chronic glomerulonephritis are not separate and distinct anatomic entities but merely represent different manifestations or phases of one and the same general pathologic process, the natural history of which is progression to termination in failure of renal function.

Progress in Internal Medicine

VASCULAR DISEASES

SEVENTH ANNUAL REVIEW

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REVIEW OF SOME OF THE RECENT LITERATURE

BY DR. VAN DELLEN AND DR. SCUPHAM

The continued interest in vascular problems and their clinical importance is evidenced by the numerous articles appearing in the world literature. Some new data have been added, with particular reference to physiologic aspects. Contributions to the medical management of patients with peripheral vascular disease have been surprisingly few, whereas many have appeared on the surgical management. We again bring to the attention of the reader the fact that this review is not complete, as many deserving articles have undoubtedly been missed.

PHYSIOLOGY

Reviews.—An excellent review of circulatory physiology was compiled by Hall.[1] He covers the large bibliography briefly but adequately, stressing the current advances in the study of the peripheral circulation and including such related topics as shock and the circulation in special regions.

Blood Flow.—Burton and Taylor[2] continue their study of the periodic fluctuations of vessel tone. They examined the changes under

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1. Hall, V. E.: Peripheral Circulation, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Stanford University Press, 1941, vol. 3, p. 343.

2. Burton, A. C., and Taylor, R. M.: A Study of the Adjustment of Peripheral Vascular Tone to the Requirements of the Regulation of Body Temperature, J. Physiol. **129**: 565 (June) 1940.

various conditions of heat loss, mainly to determine the manner in which the fluctuations were modified to maintain an appropriate value for the average blood flow. Changes in finger volume with each heart beat were used as an index of general vascular tone.

Two types of constriction were noted: that responding to external stimuli, or that of "psychic" origin, and that considered to be "spontaneous." These are distinguished by the simultaneous recording of the psychogalvanic reflex, indicating sweat gland activity and measuring vasconstriction of the "psychic type." By this method, the authors demonstrated that the sympathetic nerves to the blood vessels in the palm are completely independent of those to the sweat glands.

The regularity of the rhythm of spontaneous vasoconstriction was measured by statistical methods previously reviewed. The interval between constrictions in the "comfortable" range of environmental temperature varies from thirty seconds to two minutes, with an average of fifty to sixty seconds. As the environmental temperature is raised the average interval increases. The fluctuations are the same whether the subject is immersed in a water bath or exposed to air, an indication that the intermittence of tone is not due to a corresponding intermittence of cutaneous temperature.

The average size of each pulsation in the finger, calculated for five minute periods during both experiments, was remarkably constant. The authors also determined the average size of each pulsation between periods of vasoconstriction with rising environmental temperature and demonstrated the remarkable efficiency of temperature regulation by modifying the rhythmic fluctuations. They conclude that the reflex adjustment of the blood flow in the peripheral vessels, in accordance with the requirements of temperature regulation, is a continuous process, consisting in a corresponding modification of vascular tone, intrinsically rhythmic in character.

Spontaneous changes in volume were studied by Abramson and Katzenstein.[3] Using a standard plethysmograph, the authors were able to find these fluctuations only in the hand, since they are insignificant in the forearm, leg and foot. They occur most frequently in the young and less frequently in the old and are rather marked during sleep. They disappear at high and at low temperatures. As the authors were able to make them disappear by raising the venous pressure to 60 or 70 mm. of mercury, they conclude that the spontaneous variations in the hand are due to alterations in the caliber of the venous bed.

3. Abramson, D. I., and Katzenstein, K. H.: Spontaneous Volume Changes in the Extremities, Am. Heart J. **21**:91 (Feb.) 1941.

Stewart and Evans [4] and Abramson and Fierst [5] confirm the existing belief that blood flow is increased in hyperthyroidism. The former authors used an improved radiometer, while the latter ones used a venous occlusion plethysmograph. All report a decrease in blood flow following the administrationn of iodine or thyroidectomy. Stewart and Evans also show that in hyperthyroidism the peripheral resistance is low, almost in an inverse ratio to the basal metabolic rate.

The value of the photoelectric plethysmograph is again stressed by Hertzman and Dillon.[6] Its usefulness in distinguishing "active" from "passive" components and in separating arterial from venous reactions in the skin is suggested. In another article [7] the authors describe its clinical application and cite instances of its usefulness in studying vascular reactions in cases of Raynaud's disease or in evaluating the completeness of a sympathetic denervation.

Using the same apparatus on the tissue supplied by the radial and digital arteries, Hertzman and Dillon [8] studied the possibility of a synergistic participation of the larger arteries in the reactions of the small arteries and arterioles. Responses to a deep breath, to holding a deep breath, to the cold pressor test, to loud noises and to various psychic stimuli were noted. The participation of the radial artery in the vasoconstriction of the digital arteries is irregular but consistent in instances of massive disturbance of the circulation. The degree of constriction of the digital arteries has little predictive value with respect to the occurrence of constriction in the radial artery. The data do, however, show some selection with respect to the intensity of the participation of the radial artery in the vasomotor responses of the small arteries and the arterioles it supplies.

Dillon and Hertzman [9] report some interesting observations on the volume pulse in the finger pads of healthy subjects and contrast them with their findings in arteriosclerotic and hypertensive patients. The normal digital pulse is essentially of the same contour as the radial

4. Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow in Hyperthyroidism, Am. Heart J. **20**:715 (Dec.) 1940.

5. Abramson, D. I., and Fierst, S. M.: Resting Blood Flow in the Extremities in Hyperthyroid Subjects, Proc. Soc. Exper. Biol. & Med. **46**:39 (Jan.) 1941.

6. Hertzman, A. B., and Dillon, J. B.: Distinction Between Arterial, Venous and Flow Components in Photoelectric Plethysmography in Man, Am. J. Physiol. **130**:177 (July) 1940.

7. Hertzman, A. B., and Dillon, J. B.: Application of Photoelectric Plethysmography in Peripheral Vascular Disease, Am. Heart J. **20**:750 (Dec.) 1940.

8. Hertzman, A. B., and Dillon, J. B.: Reactions of Large and Small Arteries in Man to Vasoconstrictor Stimuli, Am. J. Physiol. **130**:56 (July) 1940.

9. Dillon, J. B., and Hertzman, A. B.: The Form of the Volume Pulse in the Finger Pad in Health, Arteriosclerosis, and Hypertension, Am. Heart J. **21**: 172 (Feb.) 1941.

pulse, with one exception; the interval between the base and the peak of the digital pulse wave, termed by the authors the "crest time," is slightly greater than that occurring in the radial pulse wave. This difference suggests that the pulse encounters slight resistance in the vessels of the hand and fingers. In cases of hypertension and arteriosclerosis the contour of the digital pulse wave is usually altered earlier and to a greater extent than that of the radial pulse, with a resultant increase in "crest time." In some young patients with hypertension and in others with hypertensive tendencies irregular vibrations are present at the catacrotic limb of the digital pulse. These changes are always less common in the radial pulse. From this evidence Hertzman and Dillon conclude that the effect of arteriosclerosis and hypertension on the dynamics of the arterial system appears in the vessels of the finger pad before it becomes apparent in the radial artery. The differences between the contour of the digital and that of the radial pulse represent differences in the elastic properties of the vessels. The photoelectric plethysmograph is also being used in England by Leibel[10] and by Squire.[11] Many of the earlier observations of Hertzman are confirmed and modifications in technic are suggested by these authors.

Capillaries.—Sanders, Ebert and Florey[12] studied capillary contraction and were unable to find evidence to support the existing view that Rouget cells participate in this process. Using improved methods and higher magnification, they observed capillaries in newly grown tissue of extreme thinness contained in chambers attached to rabbits' ears. They report that the capillaries contract independently of the Rouget cells. This phenomenon was visible in all of the capillaries studied. As the authors were able to induce contractions at will by stimulating the peripheral end of the cut cervical portion of the sympathetic trunk, they conclude that these contractions are under the control of the sympathetic nervous system. Endothelial swelling can obliterate the vessels. In venules, after mild trauma, "spikes" appear to form on the endothelial surface; on these, red corpuscles are momentarily caught, thereby grossly deforming the capillary cortex.

The oxygen, carbon dioxide and lactic acid contents of venous blood were determined by Harpuder, Stein and Byer[13] in an attempt to investigate the role of the arteriovenous anastomosis in occlusive vascular

10. Leibel, B.: Peripheral Circulation by Photo-Electric Recording, Brit. Heart J. **2**:141 (July) 1940.

11. Squire, J. R.: An Instrument for Measuring the Quantity of Blood and Its Degree of Oxygenation in the Web of the Hand, Clin. Sc. **4**:331 (Oct.) 1940.

12. Sanders, A. G.; Ebert, R. H., and Florey, H. W.: The Mechanism of Capillary Contraction, Quart. J. Exper. Physiol. **30**:281 (Sept.) 1940.

13. Harpuder, K.; Stein, I. D., and Byer, J.: The Role of the Arteriovenous Anastomosis in Peripheral Vascular Disease, Am. Heart J. **20**:539 (Nov.) 1940.

disease. They assume that in this disease the anastomosis is eventually turned from an active contractile vessel into a permanently patent channel through which blood flows uncontrolled directly into the venules. Patients with normal circulation were used as controls. In resting persons with impaired circulation, the venous blood from the foot carried more oxygen, and frequently less carbon dioxide, than did the venous blood from the forearm. Under such circumstances the content of lactic acid was relatively high. In normal subjects the opposite was noted, although the results were none too consistent. The authors are of the opinion that these findings indicate a patent arteriovenous anastomosis permitting the "shunting" of blood from the arterial to the venous side. In some cases the oxygen saturation was increased after exercise, but in the majority the opposite effect was noted. The level of lactic acid, on the other hand, was consistently elevated. In many cases analysis of samples of blood taken one-half hour after exercise revealed an oxygen deficit and a high lactic acid level, indicating an inadequacy of the peripheral circulation comparable to that occurring in normal persons recovering from fatigue. Although these observations are not entirely new, it is well to appreciate the role played by the anastomoses in determining the amount of blood available to the capillary bed. Increased blood flow through an extremity in which the anastomoses are patent does not necessarily mean that the capillary circulation to the tissues is augmented.

Solutions designed to replace blood as a perfusion medium for the study of capillary circulation must contain, according to Zweifach,[14] not only appropriate chemical constituents but a suspension of formed elements, such as particles of carbon or red cells. The action of particulate matter is beneficial in that it produces a maximum distribution of the perfusate through all the vessels of the capillary bed. In the absence of red cells or carbon, the flow is restricted to the arteriovenous capillaries. By the addition of suspended matter the flow is diverted into the true capillaries. Particulate matter, especially red cells, is effective because it plugs up leaks in the walls of the vessels. Stasis in abnormally leaky vessels is considered an additional factor acting to prevent further loss of fluid by clogging these vessels and eliminating them from the active circulation.

Continuing this type of investigation, Chambers and Zweifach[15] report their observations on the permeability of capillaries in the tongue and mesentery of the frog. They believe that the kind of permeability

14. Zweifach, B. S.: The Distribution of Blood Perfusates in Capillary Circulation, Am. J. Physiol. **130**:512 (Sept.) 1940.

15. Chambers, R., and Zweifach, B. W.: Capillary Endothelial Cement in Relation to Permeability, J. Cell. & Comp. Physiol. **15**:255 (June 20) 1940.

displayed by a membrane of the endothelial type can be explained without taking into account the cellular components of the vessels, concluding that the filtration barrier is divided into two constituents: the intercellular cement and an adsorbed layer of protein. This cement is spread over the inner surface of the endothelial cells, as well as between them and is continually washed away by the blood and replaced by secretion of the endothelial cells. If the perfusion fluid is acid or lacks calcium, the cement softens and is removed more rapidly. These conditions, as well as mechanical injury, favor extrusion of formed elements and outward diffusion of the fluid of the perfusate. The cement becomes sticky, and red corpuscles adhere to the injured areas, thus plugging leaks and maintaining normal permeability. Protein from the blood is also deposited on the intercellular cement. The authors suggest that although the intercellular cement is the actual filter, the pores of the filter may be clogged by the protein. Hence, changes in the porosity of the capillary wall, to the extent of permitting the colloidal constituents of the blood to leak through, may be due to the impairment of adsorption of the serum proteins to the inner surface of the vessel.

In addition, Zweifach [16] stresses the importance of the anatomic arrangement of capillaries in the production of edema. Since only a few of the capillaries convey an active flow of blood in resting tissue, it would seem to follow that the inactive capillaries do not participate in the withdrawal of tissue fluid. The author shows that such a condition does not exist, as the presence of a circulation in the arteriovenous capillaries alone initiates a suction force which acts on the static true capillaries and therefore sets into motion a mechanism for fluid exchange between the capillary blood stream and the tissue spaces. Conditions which upset the suction prevent adequate inward diffusion and result in an excess of fluid in the tissue spaces.

Engel [17] observed the influence of the sympathetic nervous system on capillary permeability in cats, rabbits and dogs. Capillary permeability is determined by injecting fuchsin S intramuscularly or intravenously and perfusing the knee joints at various intervals to measure the amount of dye passing through the synovial membranes. One knee joint is deprived of its sympathetic innervation, and the other is used as a control. Simultaneously with perfusion, temperatures are taken by means of thermocouples inserted into the lower portions of the quadriceps muscles.

16. Zweifach, B. W.: The Structural Basis of Permeability and Other Functions of Blood Capillaries, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1940, vol. 8, p. 216.

17. Engel, D.: The Influence of the Sympathetic Nervous System on Capillary Permeability, J. Physiol. **99**: 161 (Jan.) 1941.

In the majority of both the acute and the long term experiments, in spite of marked vasodilation, excretion of dye was considerably reduced on the sympathectomized side. The amount of dye excreted did not, however, parallel temperature gradients. The author's only explanation for the phenomenon is purely factual, that sympathetic activity increases and sympathectomy decreases capillary permeability. He believes that the permeability factor counterbalances the effect of vasomotor changes.

Menkin [18] shows that an extract of the adrenal cortex is capable of inhibiting the usual effect of leukotaxine, or any inflammatory exudate, in increasing capillary permeability. This effect is easily demonstrated by adding the extract to the exudative material and injecting the mixture into the cutaneous tissue of a normal rabbit. The influence of the substance from the adrenal cortex on capillary filtration is considered by the author of possible significance in various types of shock.

Rigdon [19] suggests that epinephrine also inhibits capillary permeability because trypan blue, administered intravenously, fails to localize in areas of the skin into which epinephrine has been previously injected and which have been treated with xylene. Although it is assumed that the failure of the dye to localize is an index of capillary permeability, it is also possible that complete vascular occlusion or absorption of the dye by the impaired cells may be the primary cause.

Rigdon [20] also states that trypan blue injected intravenously into rabbits will localize and concentrate in areas of skin into which a suspension of Staphyloccocus aureus in physiologic solution of sodium chloride has previously been injected. On the other hand, the dye fails to localize in areas of skin into which killed staphylococci have been injected.

Brown [21] reports that in a series of 100 persons with scarlet fever the capillary resistance was low at the onset of the disease but increased during convalescence. The persons with the most toxic appearance and those who had most marked desquamation had the lowest capillary resistance. Those who gave a negative reaction to the Dick test also showed a lower capillary resistance. Brown is of the opinion that the increased capillary resistance in patients convalescing from scarlet fever probably due to the decreasing amount of streptococcus toxin in the circulating blood.

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18. Menkin, V.: Effect of Adrenal Cortex Extract on Capillary Permeability, Am. J. Physiol. **129**:691 (June) 1940.

19. Rigdon, R. H.: A Study of Capillary Permeability and Inflammation in the Skin of Rabbit Given Adrenalin, Surgery **8**:839 (Nov.) 1940.

20. Rigdon, R. H.: Observations on Capillary Permeability in Areas of Inflammation Produced by Staphylococci, Surgery **9**:436 (March) 1941.

21. Brown, E. E.: Capillary Resistance in Scarlet Fever, Arch. Pediat. **57**: 553 (Sept.) 1940.

Edwards and his colleagues [22] studied the cutaneous vascularity and pigmentation of 4 castrated men (including 1 Negro) and 5 eunuchoid patients. Determinations were made with the Hardy recording spectrophotometer before, during and after treatment with testosterone propionate. The skin of the castrates contained a generally diminished quantity of hemoglobin. The proportionate amount of hemoglobin in a reduced state exceeded that usually noted in the skin of normal men. This variation is interpreted as an indication that the cutaneous vascular bed of castrates, in contrast to that of normal persons, is smaller and has less blood flowing through it. Conversely, in those cutaneous areas characterized by a large venous bed, there was a greater amount of reduced hemoglobin than occurs in normal men, an indication that the veins were dilated. These changes were reversed by the administration of testosterone propionate. In the rich arterial regions of the integument, on the contrary, the volume of blood was increased, and it likewise contained more oxyhemoglobin. The reaction of the testosterone propionate began within one hour after injection and reached a maximum effect in two or three hours. Other results were reported by these authors, but as they are not related to the vascular system they will be omitted. The authors conclude that the androgens have a profound influence on the vascularity and pigmentation of the entire human skin.

Cold.—Brooks and Duncan [23] continue their experimental study of the effect of temperature on the survival of anemic tissue. They attempt to determine the minimum time for applying a pressure of 130 mm. of mercury to a rat's tail maintained at a given temperature which will insure the subsequent development of gangrene after the animal has been returned to room temperature. The apparatus employed is similar to that which the authors have previously described, except for a larger chamber, which permits experiments to be conducted on 8 animals simultaneously, and apparatus for the maintenance of constant temperatures within the range of — 5 to 40 C. Gangrene develops more rapidly at higher temperatures. When the tails of 32 rats were surrounded by environmental temperatures between 1 and 5 C. for periods varying from eighteen to ninety-six hours, gangrene did not develop except in 1 tail of the 5 submitted to confinement for ninety-six hours. The latter experiment was not continued beyond this time, as many of the animals died. Gangrene always develops when the tails are exposed to temperatures of — 5 C., even without pressure being applied.

22. Edwards, E. A.; Hamilton, J. B.; Duntley, S. Q., and Hubert, G.: Cutaneous Vascular and Pigmentary Changes in Castrate and Eunuchoid Men, Endocrinology **28**:119 (Jan.) 1941.

23. Brooks, B., and Duncan, G. W.: Effect of Temperature on Survival of Anemic Tissue: Experimental Study, Ann. Surg. **112**:130 (July) 1940.

The authors emphasize that the experiments do not yield sufficient evidence to be accepted for clinical usage, even though gangrene does not occur in all of the animals. Microscopic studies of the rats' tails revealed extensive fibrous replacement of highly specialized tissue. In addition, the rat's tail is thin and cannot be compared to the human extremity, which is relatively thick.

The penetrative effect of cold was studied by Bierman and Friedlander.[24] When ice bags were placed on each side of the human calf the surface temperature materially decreased, but the temperature of the calf muscles actually diminished as much as 26.4 F. In this study the thermocouple tip reached about 2 inches (5 cm.) below the surface of the skin. Similar experiments were carried out in other regions of the body. Cold was shown to penetrate through the cheek, from the rectum to the posterior part of the male urethra, from the vagina to the urethra and the bladder and through the abdomen, lowering the temperature of the stomach. Studies on human subjects and on animals show that cold is able to penetrate even through the skull and influence intracranial temperature. The experiments on the systemic effects of cold are well known and are not repeated. The authors make no attempt to explain their observations, nor do they suggest any further therapeutic use of cold. They cite 2 instances in which local refrigeration was applied to the extremities of patients in whom embolization of the iliac arteries occurred as a complication of severe cardiovascular disease. While both of these patients died, the cold prevented the spread of gangrene and cyanosis and thus eliminated the usual fetid odor.

The therapeutic possibilities of reduced temperatures in limb surgery are again stressed by Allen.[25] As too few clinical studies have been undertaken, the majority of his conclusions are based on animal experimentation. Refrigeration in treatment of critical conditions is feasible, as the author shows that when cold is applied to a diseased or gangrenous extremity, made bloodless by a tourniquet, the infection or toxemia no longer spreads. Refrigeration will also minimize the use of an anesthetic for future limb surgery. Allen also demonstrates, both clinically and in animal experimentation, that an extremity with normal circulation remains vitalized for a day or two after a tourniquet is applied, providing the environmental temperature is near freezing. In arteriosclerosis obliterans the same thing will occur, but for only a short time.

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24. Bierman, W., and Friedlander, M.: The Penetrative Effect of Cold, Arch. Phys. Therapy **21**:585 (Oct.) 1940.

25. Allen, F. M.: Reduced Temperatures in Surgery: I. Surgery of Limbs, Am. J. Surg. **52**:225 (May) 1941.

Effect of Drugs.—Using a radiometer to measure surface temperatures over various parts of the body, Stewart and Jack [26] record the changes in peripheral blood flow resulting from the intravenous injection of theophylline with ethylenediamine. In 21 of 25 cases 0.48 Gm. of the drug induced a transitory rise in blood flow, an effect which could be increased with greater rapidity of injection. As blood flow increased, the cutaneous temperature decreased, mainly because of sweating, and as the skin became cooled the body lost heat. The cutaneous temperature of the hands and feet varies more than that of other parts of the body but is not an index of the average body temperature. Additional studies of the effect of theophylline with ethylenediamine on oxygen consumption and cardiac output revealed that the latter is increased, whereas the former remains unchanged.

Studies of the effect of nicotinic acid on the peripheral circulation have been reviewed previously. Vasodilatation in the extremities was found to be minimal. Recently, Abramson, Katzenstein and Senior [27] studied the effect of this substance on the peripheral blood flow by means of the standard plethysmograph. In 15 subjects maintained on well balanced diets, the blood flow increased significantly in the hand and forearm, but only slightly in the leg. Since the changes in peripheral circulation were not accompanied by any definite or consistent alteration in blood pressure or pulse rate, the authors consider it probable that the effect is due to local changes in the blood vessels rather than to an increase in cardiac output.

Bean and Spies,[28] who have reported little increase in surface temperature of the extremities, discourage the use of nicotinic acid in the treatment of peripheral vascular disease. They also studied all of the chemicals related to nicotinic acid and found their vasodilating action to be similar. These include the sodium, ammonium, ethyl and monoethanolamine salts of nicotinic acid, as well as pyridine and pyrazine compounds. No vasodilatation followed the administration of certain related pyridine or pyrazine compounds, too numerous to include in this review.

During the past year two new drugs having vasodilating properties were introduced. Unfortunately, neither yields satisfactory results.

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26. Stewart, H. J., and Jack, N. B.: The Effect of Aminophyllin on Peripheral Blood Flow, Am. Heart J. **20**:205 (Aug.) 1940.

27. Abramson, D. I.; Katzenstein, K. H., and Senior, F. A.: Effect of Nicotinic Acid on Peripheral Blood Flow in Man, Am. J. M. Sc. **200**:96 (July) 1940.

28. Bean, W. B., and Spies, T. D.: A Study of the Effects of Nicotinic Acid and Related Pyridine and Pyrazine Compounds on the Temperature of the Skin of Human Beings, Am. Heart J. **20**:62 (July) 1940.

being less efficient than those already acceptable. Unna [29] studied the antispasmodic action of a new synthetic compound, the hydrochloride of an amino acid ester (benzyl betadimethylaminoalphaphenylalphaethylpropionate hydrochloride), on common laboratory animals and concluded that in its effect on the vascular tree the drug has few advantages over papaverine, other than a lower toxicity. Popkin [30] found the new synthetic papaverine-like drug cyverine hydrochloride (di-[β-cyclohexylethyl] methylamine hydrochloride) to have a negligible effect on the surface temperature, oscillometric index and clinical improvement of 12 persons suffering from an occlusive vascular disease. In addition, it frequently caused unpleasant symptoms, such as heart burn, headache and dizziness.

Kling [31] studied the efficiency of histamine, mecholyl chloride (acetylbetamethylcholine hydrochloride) and doryl (carbaminoylcholine chloride) as vasodilators, using two methods of application. Employing the triple response method described by Lewis, he reports that a 1:1,000 solution of histamine phosphate gives a far stronger wheal and flare than a 1:100 solution of either mecholyl chloride or doryl. By cataphoresis, the full effect of histamine is reached within five to ten minutes, and at that time the rise in the temperature of the skin is greater than that induced by mecholyl. On the other hand, when the treatment is prolonged a somewhat higher and more protracted duration of rise in cutaneous temperature follows cataphoresis of mecholyl because of the more pronounced systemic reaction. Kling considers the latter reaction undesirable, and possibly dangerous. The fact that doryl can induce even a greater systemic reaction makes it unsuitable for iontophoresis. It is the author's opinion that histamine is the drug of choice for the production of local vasodilatation without systemic reaction.

Behnke and Willmon [32] show that helium is capable of diffusing inward through the skin at a rate increasing with temperatures in the range of 28 to 35 C. Above 28 C. the increase in absorption of helium is easily correlated with the rise in peripheral blood flow. Computation of

29. Unna, K.: A Pharmacological Study of a New Synthetic Anti-Spasmodic, Benzyl B-Dimethylamino-Phenyl-Ethyl-Propionate Hydrochloride, J. Pharmacol. & Exper. Therap. **70**:179 (Oct.) 1940.

30. Popkin, R. J.: Cyverine Hydrochloride, a New Synthetic Papaverine-Like Compound: A Report on Its Vasodilator Action in Chronic Occlusive Peripheral Vascular Diseases, J. Pharmacol. & Exper. Therap. **71**:320 (April) 1941.

31. Kling, D. H.: Response and Increase in Skin Temperature as Indicators of Efficiency of Vasodilating Drugs by Iontophoresis, Arch. Phys. Therapy **21**: 389 (July) 1940.

32. Behnke, A. R., and Willmon, T. L.: Cutaneous Diffusion of Helium in Relation to Peripheral Blood Flow and the Absorption of Atmospheric Nitrogen Through the Skin, Am. J. Physiol. **131**:627 (Jan.) 1941.

the flow on the basis of helium transport from the periphery to the lungs gives values of the same order as those computed by Hardy and Soderstrom on the basis of heat lost from the body. In addition, Behnke and Willmon demonstrated that nitrogen is capable of diffusing inward through the skin, but in somewhat less than 50 per cent of the amount of helium absorbed under similar conditions.

Oscillometry.—The value of oscillometry in making a diagnosis of nonpalpable aneurysm of the peripheral artery is reported by Theis.[33] He is of the opinion that an aneurysm should always be suspected whenever a local high oscillometric reading occurs in the presence of lower readings elsewhere in an extremity. In the case reported by Theis, the oscillometric reading at the knee was double that obtained either above or below that point. A diagnosis of popliteal aneurysm was made and later was confirmed from a study of the amputated leg.

Cutaneous Temperature.— Kirklin, Plummer and Sheard[34] record an elevated surface temperature of the toes and fingers of patients with high basal metabolic rates. With a reduction in the metabolic rate, induced either by administration of compound solution of iodine U. S. P. or by partial thyroidectomy, the temperature of the toes decreases. Only minor reduction occurs in the temperature of the fingers. Although for many years clinicians have known this to occur, the authors performed these experiments to emphasize further the rôle of the extremities, particularly of the lower extremities, in the regulation of the dissipation of heat from the body.

ARTERIOSCLEROSIS

Hines and Barker[35] present an excellent review on arteriosclerosis obliterans, incorporating a clinical study of 280 cases. They supplement the clinical data with results of a detailed gross and histologic study of the arteries obtained from 32 legs that were amputated because of this disorder. They found that arteriosclerosis occurs predominantly among men between the ages of 50 and 70 years. It is six times as frequent in men as in women. There is no significant difference in racial incidence, 8.3 per cent of the patients being Jews. This is contrasted with the higher incidence of Jews among the patients having thromboangiitis

33. Theis, F. V.: Peripheral Arterial Aneurysm: Diagnosis, Prognosis and Treatment, Internat. Clin. **2**:205 (June) 1940.

34. Kirklin, O. L.; Plummer, W. A., and Sheard, C.: Measurements of the Skin Temperatures of the Extremities in Exophthalmic Goiter, Before and After Medical and Surgical Treatment, Proc. Staff Meet., Mayo Clin. **15**:774 (Dec. 4) 1940.

35. Hines, E. A., and Barker, N. W.: Arteriosclerosis Obliterans: A Clinical and Pathological Study, Am. J. M. Sc. **200**:717 (Dec.) 1940.

obliterans. The authors emphasize the possible etiologic role of certain metabolic and chemical disturbances, particularly deranged metabolism of fat and cholesterol. The lesions found in the arteries which were examined for pathologic changes consist essentially of three components: (1) atheromatous plaques in the subintimal tissue; (2) degenerative changes in the medial coat, and (3) thrombosis. No significant difference is noted in the lesions of arteriosclerosis obliterans in diabetic patients and those occurring in nondiabetic patients. No direct relation is noted between the extent of calcification and thrombosis with occlusion. On the other hand, a marked difference in the frequency of calcification exists between the sexes. The incidence of calcification among men is 69 per cent and among women 31 per cent. Comments on diagnosis and treatment are made, most of which have been included in previous reviews.

While studying the effect of spasm on the arteries in ergot poisoning, Kaunitz [36] noted the similarity of the pathologic changes to those seen in cases of arteriosclerosis. From this he postulates that angiospasm plays an etiologic role in the production of arteriosclerosis. The relation between hypertension and arteriosclerosis is well known, but Kaunitz suggests that perhaps the angiospasm which produces the hypertension also produces the arteriosclerosis. Specimens of the vessels in cases of fatal ergotism are shown to have several features in common with arteriosclerotic vessels. It is the author's opinion that the spasm of the vessel compresses the vasa vasorum and mural lymph spaces and that the compression, if prolonged, may interfere with the nourishment to the vessel wall and lead to degenerative changes, such as hyalinization, fibrosis and atheromatous degeneration characteristic of arteriosclerosis.

The effect of high protein diets and vitamins on experimental atherosclerosis of rabbits was recently reported. Flexner, Bruger and Wright [37] state that thiamine hydrochloride and ascorbic acid do not influence the cholesterol content of the blood of rabbits fed cholesterol and that these vitamins neither enhance nor inhibit cholesterol atherosclerosis of the aorta. Meeker and Kesten,[38] in studying the effect of protein on experimental atherosclerosis, noted that a high protein diet containing soybean flour diminishes the incidence and degree of experimental sclerosis in rabbits fed cholesterol, whereas a high protein diet containing defatted

36. Kaunitz, J.: Importance of Angiospasm in Development of Arteriosclerosis, M. Rec. **152**:106 (Aug. 7) 1940.

37. Flexner, J.; Bruger, M., and Wright, I. S.: Experimental Atherosclerosis: Effect of Thiamine Hydrochloride and Ascorbic Acid on Experimental Atherosclerosis in Rabbits, Arch. Path. **31**:82 (Jan.) 1941.

38. Meeker, D. R., and Kesten, H. D.: Effect of High Protein Diets on Experimental Atherosclerosis of Rabbits, Arch. Path. **31**:147 (Feb.) 1941.

casein increases the degree of sclerosis. In rabbits given the high protein, defatted casein diet alone hypercholesteremia and atheromatous lesions of the aorta developed, indistinguishable from those produced by cholesterol alone.

Keith and Horton [39] report 3 cases of intermittent claudication associated with sclerotic lesions of the abdominal aorta. The site of pain in these cases was chiefly the upper part of the legs and the hips; pain was initiated by walking and was relieved by a short period of rest. In all 3 cases the authors were able to demonstrate arteriosclerotic changes in the abdominal aorta, decrease or absence of pulsations in the arteries of the involved legs and abnormal thermal responses in the toes to changes in environmental temperature.

THROMBOSIS AND EMBOLISM

Lowenberg [40] reports 3 cases of acute traumatic arterial thrombosis. In each case the involvement was unilateral, was of sudden onset and occurred in a person who was previously healthy and had none of the usual prodromal symptoms of arterial insufficiency. It is Lowenberg's opinion that chronic trauma produces a latent arteritis which acts as the predisposing cause. This was particularly true in 2 of the cases, but in the third one trauma occurred thirty years prior to the onset of thrombosis. In all cases the degree of vasospasm was high, but later, after the patients became asymptomatic, examination revealed definite arterial obliteration.

Gangrene as a complication of scarlet fever is rather rare. Breen [41] and Hoyne and Smollar [42] each report a case in a 4 year old child. In the case described by the last-named authors panarteritis of most of the arterioles was noted in the pathologic specimen.

A case of gangrene of the hand following the intravenous administration of neoarsphenamine is reported by Newman and Giles.[43] A study of the vessels in the amputated extremity revealed complete occlusion of the radial, ulnar and interosseous arteries but no abnormality of the vessels proximal to those involved. The drug had probably been administered into the brachial artery.

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39. Keith, N. M., and Horton, B. T.: Intermittent Claudication Associated with Sclerotic Lesions of the Abdominal Aorta, Internat. Clin. **2**:21 (June) 1940.

40. Lowenberg, E. L.: Acute Traumatic Arterial Thrombosis of the Extremities, Virginia M. Monthly **67**:630 (Oct.) 1940.

41. Breen, G. E.: Gangrene in Scarlet Fever, Lancet **2**:196 (Aug. 17) 1940.

42. Hoyne, A. L., and Smollar, L.: Gangrene as a Complication of Scarlet Fever: Report of a Case with Panarteritis, J. Pediat. **18**:242 (Feb.) 1941.

43. Newman, L. H., and Giles, H. D.: Case Report of Gangrene of the Hand Due to Neoarsphenamine Injection, Ohio State M. J. **36**:961 (Sept.) 1940.

Kaufman [44] reports a case of gangrene of the finger following digital nerve block anesthesia. Although this complication of local anesthesia is not unknown among surgeons, few cases have been noted in the literature. Little is known of its cause. The author suggests that its prophylaxis is possible and lays special stress on avoiding the use of epinephrine and the tourniquet.

Two cases of gangrene of unknown cause were reported by Marshall.[45] In both cases the ears, fingers and toes were involved. In 1 case the patient was a man aged 53 and in the other a boy aged 5. Both recovered.

Leriche [46] describes a syndrome occurring with an occlusion of the terminal portion of the aorta by thrombosis. It is characterized by five symptoms: loss of penile erection; extreme lassitude and fatigability of both lower extremities; complete atrophy of both lower extremities; pallor of the skin of the feet and legs even during dependency, with an ivory or marble appearance during elevation, and the absence of pulsations in the leg and thigh. As a rule the toes maintain a good appearance, and the nails and skin show little evidence of nutritional dysfunction. Cyanosis of the feet and legs occurs in the terminal phases, with desquamation of the skin, ulcer formation at points of pressure, usually preceded by ecchymosis, and, ultimately, gangrene with extreme pain. The diagnosis can be confirmed by arteriographic examination. Leriche includes in his description reports of 2 cases of aortic occlusion.

Many other cases of thrombosis of the abdominal aorta were reported during the past year. Of these, 2 are of interest. Brewster [47] reports a case in which the aorta was obstructed by a saddle thrombus associated with obstruction of the inferior vena cava by an enlarged mass of malignant lymph glands. In the case reported by Ronald and Leslie [48] "regional" signs and symptoms were absent. At autopsy no clinical evidence of impaired circulation in the extremities or evidence of collateral circulation could be found.

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44. Kaufman, P. A.: Gangrene Following Digital Nerve Block Anesthesia: Report of a Case, Arch. Surg. **42**:929 (May) 1941.

45. Marshall, R.: Two Cases of Peripheral Gangrene of Unknown Origin, Brit. M. J. **1**:886 (June 1) 1940.

46. Leriche, R.: De la résection du carrefour aortico-iliaque avec double sympathectomie lombaire pour thrombose artéritique de l'aorte; le syndrome de l'oblitération termino-aortique par arterite, Presse méd. **48**:601 (July 24-27) 1940.

47. Brewster, E. S.: Obstruction of the Abdominal Aorta and the Inferior Vena Cava Due to "Saddle Thrombus" and Tumor Mass Respectively, J. Iowa M. Soc. **31**:12 (Jan.) 1941.

48. Ronald, J., and Leslie, M.: Thrombosis of the Abdominal Aorta, Glasgow M. J. **84**:7 (July) 1940.

Koucky and his associates [49] attempt to evaluate various therapeutic measures employed in 25 cases of peripheral arterial embolism in a large charity hospital. Only statistical data will be mentioned at this time, as the therapeutic measures are considered more fully in the surgical section of this review. Most of the cases of embolism occurred in late adult life. In 2 cases the patients were less than 10 years of age, and in 2 others they were between 70 and 80 years. In this series, mitral heart disease, on the basis of subacute bacterial or chronic rheumatic carditis, was the direct etiologic agent. The lower extremities were more frequently involved than the upper ones, the ratio being 5 : 1.

THROMBOANGIITIS OBLITERANS

Tetelbaum [50] employed arteriography in studying 31 cases of thromboangiitis obliterans. This method permits him to determine the degree of narrowing of the arterial lumen, the localization of the constriction and the state of the collateral vessels. It is his opinion that in no other way can the level of the thrombosing process and the degree of the development of the collateral circulation be determined. In some cases he was able to substitute sympathectomy for amputation. If amputation is indicated, the arteriograph will suggest the optimum level. The author urges recourse to arteriography in cases of difficult differentiation between functional and organic disease of the blood vessels.

Theis and Freeland [51] studied the effect of tobacco smoking on the oxygen saturation of the arterial blood in patients with thromboangiitis obliterans and in normal subjects. They noted that smoking is usually accompanied by a greater reduction in the oxygenation of the arterial blood in the former group than in the latter. The extent of reduction seems to be influenced by physiologic adjustments in the blood pressure, pulse rate and peripheral cutaneous temperature. When no adjustment occurs the oxygen saturation of the arterial blood is occasionally found to be elevated. The increased oxygenation is greatest in patients who have recovered from thromboangiitis obliterans and who, after a period of abstinence from smoking, have extremely low oxygen saturation.

It is the author's suggestion that the etiologic factor in thromboangiitis obliterans may be a failure of physiologic adjustment to compensate for the lowered oxygen tension in the tissues.

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49. Koucky, J. J.; Beck, W. C., and Hoffman, J. M.: Peripheral Arterial Embolism, Am. J. Surg. **50**:39 (Oct.) 1940.

50. Tetelbaum, E. G.: Arteriography in Obliterating Thrombo-Angiitis, Vestnik khir. **59**:464 (May) 1940.

51. Theis, F. V., and Freeland, M. R.: Smoking and Thrombo-Angiitis Obliterans, Ann. Surg. **113**:411 (March) 1941.

A case of thromboangiitis obliterans involving the spermatic arteries was reported by Mathé.[52] The thrombosis produced an anemic infarct of the central segment of the testis, resulting in a swelling indistinguishable on physical examination from a tumor.

ARTERITIS

Warshawsky [53] reports a case of doubtful syphilitic endarteritis obliterans in a young man with involvement of all extremities and gangrene of one toe. In spite of adequate antisyphilitic therapy, recovery took place in the usual time for any obliterative lesion. As a biopsy was not performed, a procedure most essential for diagnosing this condition, we believe that this case is indistinguishable from one of thromboangiitis obliterans.

A case of mycotic aneurysm of the femoral artery is reported by Schäfer.[54]

During the past year cases of temporal arteritis were reported by Bowers,[55] Sprague and MacKenzie [56] and Scott and Maxwell.[57] A total of 18 cases is now on record. In the case reported by Bowers, prompt relief followed the removal of a segment for biopsy. He considers this significant, as relief was probably obtained by interrupting the sympathetic nerve pathway.

TUMORS OF BLOOD AND LYMPH VESSELS

Watson and McCarthy [58] made a study of 1,056 patients with 1,363 benign tumors of lymph and blood vessels, including 1,308 hemangiomas, 41 lymphangiomas and 14 hygromas. Evidence of a tumor was present in 73 per cent of the patients at birth and developed in 85 per cent before the end of the first year. The authors propose the following classification of hemangiomas, based on clinical, pathologic and therapeutic considera-

52. Mathé, C. P.: Thrombo-Angiitis Obliterans (Buerger's Disease) of the Spermatic Arteries: Report of a Case, J. Urol. **44**:768 (Dec.) 1940.

53. Warshawsky, H.: Syphilitic Endarteritis Obliterans, M. Bull. Vet. Admin. **17**:421 (April) 1941.

54. Schäfer, A.: Kriegschirurgische Beobachtung eines mykotischen Aneurysma der Arteria femoralis, Zentralbl. f. Chir. **68**:6 (Jan. 4) 1941.

55. Bowers, J. M.: Arteritis of the Temporal Vessels, Arch. Int. Med. **66**:384 (Aug.) 1940.

56. Sprague, P. H., and MacKenzie, W. C.: A Case of Temporal Arteritis (Horton-Magath Syndrome), Canad. M. A. J. **43**:562 (Dec.) 1940.

57. Scott, T., and Maxwell, E. S.: Temporal Arteritis: A Case Report, Internat. Clin. **2**:220 (June) 1941.

58. Watson, W. L., and McCarthy, W. D.: Blood and Lymph Vessel Tumors, Surg., Gynec. & Obst. **71**:569 (Nov.) 1940.

tions: capillary hemangioma; cavernous hemangioma; angioblastic, or hypertrophic, hemangioma; racemose hemangioma; diffuse systemic hemangioma; metastasizing hemangioma; naevus vinosus, or port wine stain, and hereditary hemorrhagic telangiectasis (Rendu-Osler-Weber disease). Lymphangiomas, like hemangiomas, may possess marked capacity for growth and are not, as was once supposed, dilated static normal lymph channels. Of the 41 lymphangiomas, 61 per cent were present at birth and 95 per cent were observed before the age of 10. Tumors of this type have been classified into five divisions: simple lymphangioma; cavernous lymphangioma; cellular, or hypertrophic, lymphangioma; diffuse systemic lymphangioma and cystic hygroma, or cystic lymphangioma. The tumor definitely develops from lymphatic tissue in the neck, axilla, retroperitoneal tissues or groin. Hygromas are generally present at birth and grow rapidly. Thirteen of the fourteen tumors of this type were located in the neck; the other one was in the axilla.

Cases of glomus tumors were reported by Raisman,[59] Hoffmann and Ghormley,[60] Kirby,[61] Swenson[62] and Lucinescu, Repciuc and Diaconescu.[63] The largest group of cases is reported by Raisman, who found 12 tumors in 11,000 pathologic specimens examined over a period of seven years.

PERIARTERITIS NODOSA

As several hundred cases of periarteritis nodosa are now recorded in the medical literature, we are of the opinion that additional case reports are unnecessary.

An excellent review of periarteritis nodosa is submitted by Grant.[64] In addition to reporting 7 cases, he suggests that the condition is much less rare than is commonly thought and is not necessarily fatal. Grant believes that if one is to familiarize himself with the general features of the disease, a diagnosis can be made in many instances at the bedside. Unfamiliarity with the disease probably accounts for its assumed rarity.

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59. Raisman, V.: Glomus Tumors (Angio-Neuro-Myoma), Bull. Hosp. Joint Dis. **1**:107 (Oct.) 1940.

60. Hoffmann, H. O. E., and Ghormley, R. K.: Glomus Tumor and Intramuscular Lipoma: Report of Two Cases, Proc. Staff Meet., Mayo Clin. **16**:13 (Jan. 2) 1941.

61. Kirby, D. B.: Neuromyoarterial Glomus Tumor in Eyelid, Arch. Ophth. **25**:228 (Feb.) 1941.

62. Swenson, R. E.: Glomus Tumor: Report of Case, New England J. Med. **223**:1057 (Dec. 26) 1940.

63. Lucinescu, E.; Repciuc, E., and Diaconescu, M.: Ueber Glomustumoren, Zentralbl. f. Chir. **68**:312 (Feb. 15) 1941.

64. Grant, R. T.: Observations on Periarteritis Nodosa, Clin. Sc. **4**:245 (Oct.) 1940.

Lebowich and Hunt [65] stress the significance of eosinophilia accompanied by leukocytosis as a diagnostic feature in periarteritis nodosa. This combination is usually noted during the course of the disease.

CIRCULATION AND ARTHRITIS

Phemister [66] again cites instances of changes in bones and joints resulting from interruption of circulation. As these changes were nontraumatic in origin, an attempt was made to ascertain the cause. In 2 cases, of which only 1 was described in detail, the bone infarcts were secondary to caisson disease. This diagnosis was confirmed by surgical excision. In another case, an old calcified infarct of the tibia was noted in a patient with advanced arteriosclerosis, on whom autopsy was performed. While there was no direct proof that arteriosclerosis was the cause of the infarction, it appears to be the most plausible explanation. Phemister reports 2 cases in which bone infarct and chronic hypertrophic arthritis, both apparently of long standing, occurred simultaneously and suggests that an etiologic relation exists between the two conditions. He also reports 2 other cases, in which he considers some type of vascular insufficiency capable of producing, in one case, aseptic necrosis in the head of the femur and, in the other, necrosis of the lunate bone.

Steinbrocker and Samuels [67] evaluated the arterial circulation of the lower extremities in patients with chronic arthritis. Their results were not unlike those noted by many previous investigators, namely, that little relation exists between the location of the arthritic process and the site of the vascular disturbance. Some vascular abnormalities, usually vasomotor in nature, occurred in 65.9 per cent of all patients suffering from rheumatoid arthritis, but in only 35.2 per cent of all patients with osteoarthritis. The high incidence of vasomotor disturbances was considered to be secondary to some systemic reaction, probably acting through the sympathetic nervous system, although in some cases a local reflex vasospastic mechanism in the painful arthritic extremity could not be ruled out.

In a control group of 86 patients with advanced organic arterial disease, 32 per cent had a history, physical signs or roentgenographic evidence of rheumatic or arthritic involvement at some time. This incidence approximates that of such ailments in similar age groups of

65. Lebowich, J., and Hunt, H. D.: The Diagnostic Significance of Eosinophilia in Periarteritis Nodosa, Am. J. Clin. Path. **10**:642 (Sept.) 1940.

66. Phemister, D. B.: Changes in Bones and Joints Resulting from Interruption of Circulation: II. Nontraumatic Lesions in Adults with Bone Infarction; Arthritis Deformans, Arch. Surg. **41**:1455 (Dec.) 1940.

67. Steinbrocker, O., and Samuels, S. S.: The Arterial Circulation of the Lower Extremities in Chronic Arthritis, J. Lab. & Clin. Med. **26**:974 (March) 1941.

persons without arterial disturbances and contributes clinical evidence that pronounced arterial disease alone does not usually produce arthritic signs and symptoms.

RAYNAUD'S DISEASE

Three fatal cases of Raynaud's disease with scleroderma are reported by Linenthal and Talkov.[68] Roentgenograms revealed areas of fibrosis in the bases of both lungs. The authors suggest that the pulmonary fibrosis was secondary to changes in the small vessels of the lungs as a part of Raynaud's disease and was a demonstration of the generalized arterial involvement which may occur in this disease. Unfortunately, they were unable to demonstrate the pathologic changes, as postmortem examination was not permitted in any of the 3 cases.

Johnson [69] studied the clinical manifestations and results of treatment in 22 patients with Raynaud's symptoms. His observations on this series of patients confirm Hutchinson's statement, made fifty years ago, that what is known as Raynaud's disease is not a clinical entity and that the peripheral manifestations observed are merely symptoms of some more fundamental disease. This point of view is illustrated by the successful management of several patients by treating such coexisting conditions as anemia or syphilis. In 1 case the attacks completely disappeared after the patient's mental anxiety was relieved. In 5 cases various surgical procedures performed on the sympathetic nervous system were therapeutic failures, whereas in a few of them medical management gave considerable relief. In those patients undergoing surgical treatment, the cutaneous temperature remained elevated, but the symptoms continued. Thermal studies following nerve block revealed that the vessels were fully capable of further dilatation.

Johnson reviewed the various opinions regarding the nature and cause of the vascular phenomena observed in attacks of Raynaud's disease. This difference in opinion is recognized in the modes of treatment, which continue, none too successfully. He introduces a new opinion based on the assumption that the vascular changes are not necessarily due to active vascular constriction, but that they may be the result of vasodilatation in the palmar arch, with a diversion of blood from the fingers and a passive collapse of the digital vessels. In support of this idea he presents many data, the most notable of which are as follows: (1) During an attack of Raynaud's disease the radial pulse remains unchanged; (2) a vasodilating drug, such as amyl nitrite, can produce vasodilatation in one place and passive vasoconstriction in another, pro-

68. Linenthal, H., and Talkov, R.: Pulmonary Fibrosis in Raynaud's Disease, New England J. Med. **224**:682 (April) 1941.

69. Johnson, C. A.: A Study of the Clinical Manifestations and the Results of Treatment of Twenty-Two Patients with Raynaud's Symptoms, Surg., Gynec. & Obst. **72**:889 (May) 1941.

viding it causes sufficient diversion of blood to one area with a continued fall in blood pressure, and (3) after a median nerve block at the wrist, vasodilatation is known to occur in the first three fingers, to be slight in the fourth and usually to decrease in the fifth, with a fall in the cutaneous temperature of the last-named finger.

VASOSPASTIC DISORDERS

That the autonomic nervous system has representation in the cerebral cortex is suggested by Pilcher, Wyatt and Carney.[70] They observed a patient who had spastic right hemiplegia, with absence or diminution of pulsations in all of the major arteries on the involved side. The blood pressure and oscillometric index were also lowered on that side. Surgical treatment was advised, and at the time of operation an extensive cerebral infarction was found, involving a major portion of the distribution of the left middle cerebral artery. Continued observations on various autonomic functions showed evidence of unilateral overactivity of the sympathetic nervous system.

An excellent review of the available literature on cervical rib is presented by Holling,[71] with special reference to the theories of causation of symptoms. It is his opinion that the vascular symptoms are secondary to the damage of the arterial wall by the cervical rib. From his own observations and from those of other authors he concludes that the subclavian artery is compressed by the cervical rib at the lateral border of the scalenus anticus or between the anterior end of the rib and the clavicle. In 2 of the cases he reports the latter phenomenon was noted at operation. In a third case the patient had no vascular symptoms but desired relief from a peculiar clicking noise in her shoulder. At the time of operation it was noted that when the arm was adducted the clavicle slipped over the expanded anterior end of the rib with a loud click. The subclavian artery escaped compression because of its unusual lateral position. In all 3 cases relief was obtained after the cervical rib was removed.

Belgrano [72] studied 31 cases of cervical rib and 6 of hypertrophy of the transverse process of the fourth cervical vertebra. In 30 cases the patients were females, and in 7 they were males. Trauma was the cause in 6 cases. Vascular or neurologic manifestations were present in 25 cases. The most frequent symptoms were unilateral or bilateral pain

70. Pilcher, C.; Wyatt, T. E., and Carney, H. M.: Infarction of the Brain with Unilateral Circulatory Changes, Arch. Neurol. & Psychiat. **45**:321 (Feb.) 1941.

71. Holling, H. E.: The Etiology of Vascular Symptoms Occurring in Cases of Cervical Rib, Guy's Hosp. Rep. **89**:285, 1940.

72. Belgrano, M.: La costa cervicale, Gior. veneto di sc. med. **14**:155 (March) 1940.

in the shoulder and arm, frequently associated with muscular atrophy; cervical pain; paresthesias; variations in local temperature, and other sensory, motor and vascular disturbances. The predominant symptom was acute headache in 1 case and cough in 5 cases. Paresis of the dome of the diaphragm occurred in 3 cases and paralysis of vocal cords in 1 case. The arterial pressure was diminished on the involved side as compared with that on the normal side. In 21 cases roentgenograms revealed the condition was bilateral.

ACROCYANOSIS

The successful treatment of a patient with acrocyanosis by a cervicothoracic sympathetic ganglionectomy indicated to Barker and Baker [73] that vasomotor impulses are the dominant factor in the production of arteriolar spasm in this disease. This statement is in contrast to those expressions of belief that the arteriolar spasm in acrocyanosis is intrinsic in the arterioles and that vasomotor impulses play a minor role in provoking the spasm. Not only do the authors present a typical case history, but they suggest an excellent differential diagnosis of this condition, stressing particularly its resemblance to Raynaud's disease and to livedo reticularis.

ACROSCLEROSIS

According to O'Leary and Waisman,[74] the diagnosis of acrosclerosis is frequently difficult and depends on the onset of the associated vasomotor symptoms. They base their observations on a survey of 64 cases. The syndrome acrosclerosis is a combination of Raynaud's phenomena with secondary scleroderma of the distal parts of the extremities and of the face and neck. These two conditions usually have their onset together, whereas in progressive diffuse scleroderma the onset is associated initially with Raynaud's syndrome and in a few years scleroderma gradually ensues over wide regions of the body. In sclerodactylia, on the other hand, the vasospastic features are initially absent, although they may follow the sclerosis after months or years.

Acrosclerosis occurs preponderantly in women, is usually absent in childhood and is accompanied by vasomotor events which are indistinguishable from manifestations of Raynaud's disease. The treatment is none too successful, but the prognosis with regard to life is favorable. The pathogenesis is only in a stage of hypothesis, as the relation between arterial obstruction and scleroderma is still obscure.

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73. Barker, N. W., and Baker, G. S.: Acrocyanosis: Effect of Cervicothoracic Sympathectomy; Report of a Case, Proc. Staff Meet., Mayo Clin. **15**:601 (Sept. 18) 1940.

74. O'Leary, P. A., and Waisman, M.: Acrosclerosis, Proc. Staff Meet., Mayo Clin. **15**:702 (Oct. 30) 1940.

RETINITIS PIGMENTOSA

Brown and Whitney [75] studied the peripheral circulation in 9 cases of retinitis pigmentosa and made oscillometric readings and biomicroscopic examination of the capillaries at the nail bed. In all 9 cases the authors found unmistakable evidence of pathologic changes in the peripheral vascular system, from which they concluded a generalized involvement existed. They feel that such capillary abnormality at the chorioretinal threshold is sufficient to produce anoxia and subsequent death of the neuroepithelium. This process could explain the pathogenesis of retinitis pigmentosa.

The authors' criteria for the diagnosis of pathologic involvement of the peripheral vascular system should be criticized. In some cases the only evidence of vascular involvement was tortuous capillary loops in the nail bed, which has previously been shown to be of no diagnostic significance.

AINHUM

Two cases of ainhum, or dactylolysis spontanea, were reported by Gerwig and Warner.[76] This peculiar disease is characterized by formation of symmetric constricting bands at the bases of the little toes, with gangrene and often spontaneous amputation of the member. It is primarily a tropical disease and occurs chiefly in adult colored males. Its cause is unknown. Pathologically, the constricting band represents proliferation and hyperkeratosis of the surface epithelium, together with fibrosis of the corium. The band appears invariably at the digitoplantar fold. The blood vessels are engorged, especially those distal to the constriction. Ultimately, obliterative endarteritis precedes spontaneous amputation. As the disease is not primarily vascular in origin, the usual therapy is of little value. Intravenous administration of iodides gives relief from pain, but amputation is the treatment of choice. In each of the cases reported by Gerwig and Werner the patient was a southern Negro who had never been out of the United States.

Johnson [77] describes a case of spontaneous congenital amputation of the fingers and toes, with an annular, ainhum-like band and constriction of the distal portion of the right leg with edema. Roentgenograms of the leg did not reveal any pathologic condition of the bone. The soft tissue had an hourglass appearance, being completely constricted by a fibrous band. Although the peripheral vessels were not palpable, the oscillometric readings were above normal. Rest made the leg smaller, and a

75. Brown, W. M., and Whitney, E. L.: Peripheral Vascular Picture in Retinitis Pigmentosa, Arch. Ophth. **24**:984 (Nov.) 1940.

76. Gerwig, W. H., and Warner, C. G.: Ainhum (Dactyolysis Spontanea): Report of Two Cases, Bull. School Med. Univ. Maryland **25**:236 (April) 1941.

77. Johnson, H. M.: Congenital Cicatrizing Bands: Report of a Case with Etiologic Observations, Am. J. Surg. **52**:498 (June) 1941.

short walk induced slight edema. Excessive walking caused a dull throbbing pain and reappearance of the hourglass contour of the leg. It is interesting to note that the patient, aged 72, had been able to live until recently a normal life, without circulatory embarrassment, and his present condition was probably the result of senility and a weakened vascular bed.

The spontaneous amputation of the digits in his case differs from true ainhum in that the former was congenital. Instances of a similar condition could not be found in an embryologic laboratory which receives many monstrosities and curiosities. The author believes that it probably represents an example of focal necrosis of the limb during the developmental embryonic stage. According to this theory, the damage occurs during the first five weeks of embryonic life, and the residua are apparent at birth. The absence of several fingers and toes may have been the result of focal necrosis in early embryonic life. Other digits had cicatrizing bands but were not spontaneously amputated because this underlying process stopped in time.

SHELTER LEGS

Within a few weeks after the bombardment of London commenced, patients with swollen legs began to consult their physicians in alarming numbers.[78] Although the swelling appears benign at its onset, it later develops into marked edema, with tense red tender skin, a condition resembling cellulitis. In some cases superficial ulcers and bullae appear, while in others the edema is associated with thrombophlebitis, which usually adds to the confusion in diagnosis. Elderly women seem to be most commonly affected. Carefully taken histories revealed that the majority of patients had been sitting and sleeping in deck chairs for long periods during the bombardment. It is believed that the wooden cross bars on the deck chairs exert a pressure on the back of the thigh or the popliteal vessels that produces a venous stasis. Londoners are informed of the necessity of getting up on their feet for several hours a day as a preventive measure. Once edema develops, it is readily treated by rest in bed.

VENOUS SYSTEM

An exercise test to be used in association with studies on venous pressure is described by Veal and Hussey,[79] who found it was helpful in distinguishing between a generalized increase in venous pressure, as noted in cases of cardiac failure, and a localized increase in pressure,

78. Shelter Legs, editorial, Lancet **2**:722 (Dec. 7) 1940.

79. Veal, J. R., and Hussey, H. H.: The Use of "Exercise Tests" in Connection with Venous Pressure Measurements for the Detection of Venous Obstruction in the Upper and Lower Extremities, Am. Heart J. **20**:308 (Sept.) 1940.

as occurs in cases of venous obstruction. The test is done as follows: With the needle from the venous pressure apparatus inserted into the antecubital or femoral vein, the patient is asked to exercise the hand or foot for one minute. This is best done by having the patient squeeze a roll of bandage placed in the palm of the hand or rise on tiptoe a number of times. In a case of venous obstruction the pressure increases after exercise, whereas in a case of cardiac failure no change is noted, although in both instances the pressure may have been originally elevated.

Ferris and Blankenhorn [80] note an increase in the venous pressure of the lower extremities in cases of obstruction of the inferior vena cava. A diagnosis of such obstruction is best made by simultaneously measuring the pressure in the veins of the arm and the pressure in the veins of the leg, without the use of exercise. In all 5 cases which the authors report, in which this type of obstruction was known to exist, the venous pressure in the lower extremities was higher than that in the upper.

Using a quantitative histologic method, Carere-Comes and Canna [81] examined morphologically and quantitatively the senile variations in the muscles of the walls of various veins of each of 38 autopsy specimens. Similarities and differences were noted in the muscles of the veins in relation to the regions explored. They noted changes in the various muscle sheaths due to old age and senile atrophy. The muscle of the vein also varies with the sex of the patient. The authors consider that the possible relation between the changes in the muscle of the vein in senility and changes in tonus and venous pressure is plausible.

Tedeschi [82] notes that with increasing age a fibromuscular thickening appears on the arterial side of the wall of veins running closely adjacent to arteries. This thickening is absent in those veins separated from the companion arteries by the interposition of fatty or fibrous connective tissue and in a vein, such as the subclavian or jugular, which has a course somewhat independent of that of the corresponding artery.

THERAPY

Saland [83] outlines a plan of treatment for acute arterial occlusions, stressing the importance of suction-pressure therapy. Twenty-nine cases

80. Ferris, E. B., and Blankenhorn, M. A.: Obstruction of the Vena Cava Inferior in Liver Abscess: A New Diagnostic Sign, Internat. Clin. **4**:1 (March) 1941.

81. Carere-Comes, O., and Canna, S.: La muscolatura delle vene nelle varie età: Ricerche di istologia quantitativa, Cardiologia **4**:283, 1940.

82. Tedeschi, C.: Fibromuscular Thickening in the Walls of Veins Adjacent to Arteries, Anat. Rec. **79**:243 (Feb. 25) 1941.

83. Saland, G.: Acute Occlusions of the Peripheral Arteries: Clinical Analysis and Treatment, Ann. Int. Med. **14**:2027 (May) 1941.

of major and 2 cases of minor arterial occlusion are reported. Because the author was able to distinguish between occlusions of embolic and those of thrombotic origin certain observations are worthy of repetition. Embolism occurred in younger patients. Sex was not a factor in the causation of occlusion, although diabetes was more prevalent in females. Auricular fibrillation was a frequent precursor of embolism, but not of thrombosis. Heart disease was the underlying condition in 100 per cent of the cases of embolism. This association with heart disease is a major factor in the prognosis, because all 15 deaths in this series of cases were due not to the peripheral vascular disease but to the underlying cardiac condition.

Gangrene developed in all of the 8 cases in which no treatment was instituted except hospitalization and, presumably, rest in bed. In this group amputation was ultimately done in 62.5 per cent of the cases, and the known mortality of all 8 cases was 62.5 per cent. Conservative therapy, consisting of rest in bed, use of reflex heat, papaverine and whisky and pavaex treatments, was given in the remaining 23 cases. In most of the cases a minimum of one hundred hours of suction-pressure therapy was administered. Under this regimen Saland was able to save the limb in 95 per cent of the cases. In the group in which treatment was given the stay in the hospital was twenty and eight-tenths days less, on the average, than that of the group in which no treatment was given.

Moss and Herrmann [84] were able to control the pain of "night cramps," commonly seen in middle-aged and elderly patients, by the oral administration of quinine sulfate. Fifteen patients were so treated, none of whom had evidence of serious vascular insufficiency. Improvement to the point of complete cessation of pain was noted within a relatively short period. In some cases return of symptoms did not follow cessation of medication or substitution of placebo capsules but in the majority of cases an exacerbation occurred.

Bennett, Hines and Krusen [85] were able to produce reflex vasodilatation in the extremities by applying short wave diathermy to the trunk. Various methods of application were tried, but the use of the electromagnetic cable in a pancake formation under the lumbosacral region was found to be the most simple and comfortable. Twenty observations were made, and in each instance the lower extremities became warmer. The use of diathermy as a test for vasospasm is dis-

84. Moss, H. K., and Herrmann, L. G.: Use of Quinine for Relief of "Night Cramps" in the Extremities, J. A. M. A. **115**:1358 (Oct. 19) 1940.

85. Bennett, R. L.; Hines, E. A., and Krusen, F. H.: Effect of Short-Wave Diathermy on the Cutaneous Temperatures of the Feet, Am. Heart J. **21**:490 (April) 1941.

couraged. The authors are aware of the dangers of this form of therapy and suggest that it be used only under careful medical supervision.

Rothberg [86] treated a patient with Raynaud's disease by roentgen irradiation of the cervical and lumbar regions. Symptomatic relief was noted for two consecutive winters. As the patient had a recurrence of symptoms six months later, additional radiation was given, which allowed her freedom from pain and ulcers for the remainder of the winter.

ABNORMALITIES OF BLOOD PRESSURE

The question as to what constitutes normal blood pressure is still under discussion. The paper by Robinson and Brucer,[87] which was reviewed last year, has aroused some criticism, particularly in regard to the statistical methods employed in arriving at the conclusions. The author [88] of the criticism states that his objections do not center about the acceptability to physicians of the conclusions reached, but about the validity of the statistical proof offered.

Robinson [89] further continues the argument in regard to the "ideal normal blood pressure," which in his opinion is below 110 mm. of mercury systolic and 70 diastolic. Such pressures were found in 25 per cent of 10,833 persons. Thirty-four per cent had diastolic pressures below 70 mm. Pressures of this type had little relation to age until the age of 70 years was reached; then the incidence seemed to decrease. Young women were more numerous in this low pressure group, but the incidence in older women was about the same as that in men of similar age. Weight seemed to be a much more important factor than sex, and persons of light weight, regardless of sex, were more common in the low blood pressure group. Another interesting point noted was that low pressures show less fluctuation; even the yearly variation was less erratic than that of higher pressures. The author insists that low pressure has no characteristic symptomatology. Neither excessive fatigue nor lowered vitality and energy were noted in the low pressure group. In fact, these symptoms were more frequent in the high pressure group. When organic disease is excluded, such low pressure is associated with a mortality rate lower than that for average pressures.

86. Rothberg, A. S.: The Relief of Symptoms in Raynaud's Disease by Roentgen Therapy, Am. J. Roentgenol. **45**:412 (March) 1941.

87. Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure: A Statistical and Clinical Study of 11,383 Persons, Arch. Int. Med. **64**:409 (Sept.) 1939.

88. Treolar, A. E.: Normal Blood Pressure, Arch. Int. Med. **66**:848 (Oct.) 1940.

89. Robinson, S. C.: Hypotension: The Ideal Normal Blood Pressure, New England J. Med. **223**:407 (Sept. 12) 1940.

The relation between body build and hypertension has also been studied by Robinson and Brucer.[90] The controversy in regard to the relation between these factors has not yet been satisfactorily decided. These authors are convinced that one does exist. That is, men and women of broad build show a marked tendency to hypertension. The systolic pressures have a definite tendency to increase directly with the chest/height ratio. While the proportions are not exactly the same in the two sexes, linear build (low chest/height ratio) is much more frequently accompanied by low than by high pressures, both systolic and diastolic. The incidence of high pressure increases with age in men of lateral build. In men of linear (slender) build the incidence of high pressure tends to remain constant up to the seventh decade and the incidence of low pressure is constant throughout life. An increase is also observed in the average build (chest/height ratio) until the age of 50 years. After this age the average build tends to decrease. The authors believe that the chest/height ratio is a much more reliable criterion than weight under these conditions.

Observations made by Thacker[91] on a large group of university students tend to agree with those of others reporting similar work. The arbitrary blood pressure levels used in this study were 108 mm. or less, regarded as hypotensive, and 150 mm. or above, regarded as hypertensive. A control group was used whose pressures ranged from 114 to 138 mm. These three groups were subjected to a variation of the cold pressor test of Hines and Brown. It was found that normal subjects showed a more rapid response in that their pressures reached the maximum in a shorter time and returned to normal more rapidly than did the pressures of hypertensive or hypotensive subjects. Observations of other authors are in essential agreement as far as the reaction of hypertensive subjects to the cold pressor test is concerned. The same factors which are responsible for the emotional state of a person play an important role in the reactions of his blood pressure.

The author also concluded from his observations that there is a definite hereditary factor in the normal regulation of blood pressure. "The tendency toward essential hypertension or hypotension is carried by the germ plasm from one generation to the next." The use of coffee and tobacco has no significant influence on blood pressure levels. He

90. Robinson, S. C., and Brucer, M.: Body Build and Hypertension, Arch. Int. Med. **66**:393 (Aug.) 1940. Robinson, S. C.: Hypertension in Relation to Height: Its Variation with Body Build and Obesity, J. Lab. & Clin. Med. **20**: 930 (March) 1941.

91. Thacker, E. A.: A Comparative Study of Normal and Abnormal Blood Pressures Among University Students, Including the Cold-Pressor Test, Am. Heart J. **20**:89 (July) 1940.

also concluded that elevation of blood pressure should not be considered as hypertension until at least three separate observations have been made.

It has been suggested that the range of variability of blood pressure may be as important as or more important than any single reading in the determining the subsequent status in an individual case. In order to gather further information in this regard Hines [92] studied the records of 1,522 patients ten and twenty years after the original reading had been obtained. He has been of the opinion that an initial reading made under strange surroundings by a strange physician may have a significance similar to that of a reading made after the cold pressor test, in that it represents a reaction to emotional stress. As a result of these observations the idea is advanced that excessive variability from the usually normal pressure should be considered as evidence of the presence of the hypertensive state. (Hypertension is likely to develop at a later date in persons exhibiting such variability.) While Hines draws no definite conclusions on the basis of this study, he is inclined to believe that hypertension probably will not develop in persons whose pressure rises no higher than 140 systolic or 85 diastolic under nervous stress. On the other hand, persons who show even transient rises above this level are likely to display persistent hypertension subsequently. He also points out that elevation of the systolic pressure alone is not significant, but a rise above 85 diastolic is. These findings seem to hold true regardless of age. Such observations as these are significant and aid in a better understanding of the problem. Thacker [93] continued his observations on his group of students by studying the effect of exercise. His results seem to indicate that a standard exercise test yields a fairly consistent response in each of the three blood pressure groups. As a rule the increase in systolic pressure was greater in the hypertensive group than in the other two groups. The variation was considerable. Twenty per cent of the hypertensive subjects had an increase above 60 mm. of mercury, and in 2 per cent it reached 80 mm. The maximum rise for the normal subjects was 50 mm. in 82.7 per cent of cases, and in none was the increase greater than 60 mm. In persons with normal pressure such rises might have the same significance as rises obtained with the cold pressor test. The maximum rise in the hypotensive group was 40 mm., and in 91.6 per cent the rise was less than 30 mm.

The diastolic pressure decreased with exercise in all groups. Ninety-one per cent of the low pressure and normal groups did not show a

92. Hines, E. A., Jr.: Range of Normal Blood Pressure and Subsequent Development of Hypertension: A Follow-Up of 1522 Patients, J. A. M. A. **115**: 271 (July 27) 1940.

93. Thacker, E. A.: Blood Pressure Studies on University Students, Including the Effects of Exercise on Essential Hypertension, and Normal Subjects, Ann. Int. Med. **14**:415 (Sept.) 1940.

fall of more than 20 mm., and the decrease was usually less. The hypertensive subjects tended to show a greater variation in this respect also.

The return to normal of the systolic pressure occurred more rapidly in the normal than in the other two groups. Pulse rate was not a factor.

These observations are important in that they seem to indicate that the smaller the individual range of blood pressure in both systolic and diastolic levels, the less is the likelihood of hypertension developing later. That is, the lower levels of blood pressure have the least variation, and a short range of variation as the result of any stimulus must be regarded as normal.

This is further indicated by the observation that the usual pressures of the hypertensive subjects were considerably elevated above the basal pressure. Emotional factors, or the factors which govern the emotional status of a person, seem to be important in determining the blood pressure status. This agrees with the views of Hines. There certainly seems to be a hereditary relation in the tendency to high, low or normal pressure, as indicated in Thacker's groups. Work or exercise was not a factor, but increased food intake was common (two and a half times as frequent) in the hypertensive subjects.

Among the factors which result in variation of blood pressure Jacobson[94] has found that repeated contraction of a muscle group for a period of several minutes followed by complete relaxation is frequently accompanied by rises and falls both in systolic and in diastolic blood pressure. The extent of the rise and fall depends on the intensity of the effort and the ability of the subject to relax completely afterward. No rise may be obtained unless low pressure is previously brought about by complete relaxation. The more extensive the muscle contraction, the greater is the rise in pressure which follows. The author believes that emotional influences are not operative in these phenomena. This work appears to demonstrate another factor which may be an important influence in the variability both of normal blood pressure and of hypertension.

In order to obviate some of the variations in pressure, particularly those associated with the emotional effect of the actual recording, Ayman and Goldshine[95] have provided patients with the equipment for determination of their own pressures. Pressures recorded in the clinic were in general considerably higher than those recorded by the

94. Jacobson, E.: Variation of Blood Pressure with Brief Voluntary Muscular Contractions, J. Lab. & Clin. Med. **25**:1029 (July) 1940.

95. Ayman, D., and Goldshine, A. D.: Blood Pressure Determinations by Patients with Essential Hypertension: I. The Difference Between Clinic and Home Readings Before Treatment, Am. J. M. Sc. **200**:465 (Oct.) 1940.

patient at home; in some cases the difference amounted to as much as 50 to 70 mm. higher in the clinic than at home. In others the difference was not so marked, amounting to only 10 to 15 mm. in the systolic pressure. The maximum differences were noted when the home reading was taken after exercise. The diastolic pressure showed less variation, but in 23 per cent of cases there was a difference of 20 mm. or more, a striking variation. Thus it is seen that the average blood pressure as measured in the office is usually higher than that under conditions in which the patient lives, but represents in general the upper limits of the variation to which each person may be subjected.

These observations have been extended to determinations made after treatment.[96] It was thought by the writers that response to therapy was indicated by observations made at home when it was impossible to determine any result after the use of some drugs if the pressure was determined by the physician. Apparently the emotional reaction, or pressor response, is greater than the vasodilator effect of the drug. Under the ordinary conditions of the patient's life, the depressor effect may be fairly satisfactory. Apparently the observations of these authors coincide with those of Hines in regard to the emotional effect of mere taking of blood pressure as an effective stimulus which is part of the hypertensive state.

Griffith, Roberts and Corbit[97] have attempted to classify hypertension on the basis of objective observations. When the capillaries of the skin were studied most of the patients with hypertension fell into the classification of normal, although some were found who exhibited a larger number than normal of capillaries in use in a given area under average conditions. Measurement of the capillary pressure, both in normal skin and in an area of histamine flare, yielded variable results.[98] Normally, by the method used, a rise of 3 to 13 mm. of mercury occurred in the area of flare. In persons with hypertension, these results were exceedingly variable. A change of less than 3 mm. of mercury after histamine flare was thought to indicate sclerosis of the precapillary arterioles. In some instances there was an exaggerated rise of more than 13 mm. of mercury. In such cases it may be assumed that the precapillary arterioles dilated to allow the marked

96. Ayman, D., and Goldshine, A. D.: Blood Pressure Determinations by Patient with Essential Hypertension: II. The Difference Between Home and Clinic Readings During and After Treatment, Am. J. M. Sc. **201**:157 (Feb.) 1941.

97. Griffith, J. Q., Jr.; Roberts, E., and Corbit, H. O.: Studies of Criteria for Classification of Arterial Hypertension: I. Cutaneous Capillaries, Am. Heart J. **21**:47 (Jan.) 1941.

98. Griffith, J. Q., Jr.; Roberts, E., and Corbit, H. O.: Studies of Criteria for Classification of Arterial Hypertension: II. Minute Vessel Pressure, Am. Heart J. **21**:54 (Jan.) 1941.

increase in pressure from the arterial system to extend into the capillary bed. The cutaneous lymph flow [99] was found to be normal in most instances of hypertension, but it was increased in a small number of cases. Increased capillary pressure was usually present when the flow of lymph was increased.

Blood volume was most frequently found to be unchanged,[100] but in some instances an increase was noted, in which cases there was also increased capillary pressure or increased lymph flow. Increased blood volume is accounted for either on the basis of decreased vascular tone, particularly in the peripheral bed, or on a metabolic basis, which, according to the authors, indicates an increased amount of water in the blood, due either to added intake or to failure of elimination. The increase in flow in minute vessels and in lymph vessels is a compensating mechanism. Certainly increased blood volume is seldom associated with hypertension.

Griffith and his associates [101] have also attempted to evaluate the role of the pituitary gland in hypertension both by experimental observation of animals given extract of the posterior lobe of the pituitary body and by the recovery of pituitary substances from the blood of clinical patients. They found that large doses of pitressin administered to rats produced a rise in blood pressure which reached 200 mm. of mercury or more and endured for several hours. Blood volume was found to be diminished during the period of hypertension. If a single small dose of the extract was given, no change in blood volume was noted, but with repeated small doses a rise occurred. It was thought pressure might be elevated in the minute vessels, although the methods for measurement in the rats are not satisfactory. These observations were largely on cases of the type of pituitary hypertension in which increased blood volume occurred.

In the attempt to demonstrate the presence of pituitary substance in patients with hypertension, a biologic test for the presence of an antidiuretic substance in the serum was employed. The test was positive in some cases of hypertension. In such cases it was found that capillary pressure was increased; in about one half of them the lymph flow increased, and in some papilledema appeared. The blood

99. Griffith, J. Q., Jr.; Roberts, E.; Rutherford, R. B., and Corbit, H. O.: Studies of Criteria for Classification of Arterial Hypertension: III. Cutaneous Lymphatic Flow, Am. Heart J. **21**:62 (Jan.) 1941.

100. Griffith, J. Q., Jr.; Rutherford, R. B.; Roberts, E., and Lindauer, M. A.: Studies of Criteria for Classification of Arterial Hypertension: IV. Blood Volume, Am. Heart J. **21**:67 (Jan.) 1941.

101. Griffith, J. Q., Jr.; Corbit, H. O.; Rutherford, R. B., and Lindauer, M. A.: Studies of Criteria for Classification of Arterial Hypertension: V. Types of Hypertension Associated with the Presence of Posterior Pituitary Substance, Am. Heart J. **21**:77 (Jan.) 1941.

volume was either normal or increased. In such cases it was found that after irradiation of the pituitary body the test became negative and some fall in blood pressure and clinical improvement occurred. The test used in conjunction with irradiation may be considered as a guide to the effect of the process. It has little or no other value.

Graybiel and Glendy[102] did not find any significant difference in effect on blood pressure in either normal and hypertensive subjects when pitressin was administered slowly by the intravenous route. Increases in pressure were slight. The return of the pressure to the control level was somewhat slower in the hypertensive patients than in the normal ones. The authors observed constriction of the minute vessels and of the large arteries but not of the arterioles.

When the tests devised by Griffith and co-workers were applied in relation to thiocyanate therapy,[103] it was found that they furnished a fairly reliable guide to the likelihood of success with this type of treatment. If the capillary responses were normal, clinical improvement usually followed. If precapillary sclerosis was suggested by increased capillary pressure and increased lymphatic flow or if papilledema was present thiocyanate therapy usually failed. Therefore it would seem that the location of the effect is on the arteriolar structures, and if organic change in the walls of the arterioles exists release of spasm is unlikely to occur and but little fall in pressure can be expected. In general, the clinical results were as predicted.

When these observations were applied to cases in which papilledema was associated with hypertension,[104] increased intracranial tension, as measured by elevation of the spinal fluid pressure, was found. Increases in the pressure in minute vessels, cutaneous lymph flow and blood volume also occurred. In some cases there was evidence of an antidiuretic substance in the blood. In some cases renal disease was present.

It is believed that increased formation of cerebrospinal fluid is the cause of the increased intracranial pressure. This increase in quantity cannot be removed sufficiently rapidly by the blood, either because of the presence of the antidiuretic substance or because of renal failure to excrete water.

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102. Graybiel, A., and Glendy, R. E.: Circulatory Effects Following the Intravenous Administration of Pitressin in Normal Persons and in Patients with Hypertension and Angina Pectoris, Am. Heart J. **21**:481 (April) 1941.

103. Griffith, J. Q., Jr.; Lindauer, M. A.; Roberts, E., and Rutherford, R. B.: Studies of Criteria for Classification of Arterial Hypertension: VI. Treatment with Thiocyanate, Am. Heart J. **21**:90 (Jan.) 1941.

104. Griffith, J. Q., Jr.; Fry, W. E., and Roberts, E.: Studies of Criteria for Classification of Arterial Hypertension: VII. Increased Intracranial Pressure and Papilledema, Am. Heart J. **21**:94 (Jan.) 1941.

Cases of hypertension in childhood which could not be classified under any of the definitely known groups have been reported by Clark [105] and Sobel.[106] Apparently these cases would fall into the so-called essential hypertensive groups. Sobel points out that intermittent elevation of pressure in childhood tends in some cases to become more frequent and denotes incipient hypertension. In fact, the hypertensive state frequently has its origin in childhood or adolescence.

Corcoran and Page [107] present their views on the correlation of the essential aspects of clinical and experimental hypertension and suggest that angiotonin is involved in the pathogenesis of essential and malignant hypertension in man. The problem is considered from the standpoint of the four essential manifestations of hypertension, namely, those of neurogenic, endocrine, cardiovascular and renal origin. The authors point out that renin of itself is not an angiospastic substance, but when it is activated by a substance present in normal plasma, which is termed renin activator, a strong vasoconstrictor substance, which has been designated angiotonin, is produced. This differs from other vasoconstrictor substances in that it acts principally on the smooth muscle of the arterioles and on the heart. The heart responds by increased activity, particularly in the force of the beat. This response is essential because of the increased peripheral resistance offered by constriction of the arterioles. These two results are its principal effects. Thus, cardiac failure as hypertension progresses is an integral part of the disease pattern. The clinical features are progressive constriction of the arterioles, with thickening of their walls, and hypertrophy of the cardiac muscle. As these processes continue, cellular changes take place; nutrition cannot keep pace; sclerosis occurs, and finally degenerative changes result in failure of the heart, as well as in disturbances in the central nervous system, the retina and, particularly, the kidneys. The course of the disease is greatly accelerated when it is altered by the phenomena which characterize malignant hypertension, manifested pathologically by necrotizing arteriolitis. Angiotonin is believed to be capable of producing this disease pattern, resulting as it does from renal ischemia. It appears that the more rapidly renin is elaborated, the more rapid and severe is the pathologic process in the vessels.

The kidneys in cases of hypertension, as observed clinically and pathologically, follow a similar progression of changes. There is no

105. Clark, H. C.: Hypertension in Early Childhood, Am. J. Dis. Child. **59**: 353 (Feb.) 1940.

106. Sobel, I. P.: So-Called Essential Hypertension in Childhood, Am. J. Dis. Child. **61**:280 (Feb.) 1941.

107. Corcoran, A. C., and Page, I. H.: Arterial Hypertension: Correlation of Clinical and Experimental Observations, J. A. M. A. **116**:690 (Feb. 22) 1941.

apparent early functional disturbance, but its presence is indicated by the increased rate of glomerular filtration of water, as measured by inulin clearance. This increase cannot arise from the elevation of systemic arterial pressure alone and therefore must be due to increased intraglomerular pressure, which in turn is probably the result of constriction of the efferent arterioles. This view is strengthened by the fact that actually the rate of renal blood flow is decreased, another of the characteristic effects of angiotonin. The peculiar increase in glomerular function is responsible for the fact that renal function, as measured by such tests as urea clearance, remains normal in a case of hypertension, even though the disease may be far advanced. Eventually the continued vasoconstriction results in organic changes in the arterioles and occlusion takes place; glomeruli become sclerosed, and finally renal failure supervenes.

The relation of the endocrine system to this mechanism is apparently secondary. The adrenal cortex and the hypophysis are particularly important in that their secretions maintain the cardiovascular system in a state receptive to hypertensive stimuli. It seems probable that the central nervous system may play a dual role in that both reflex and psychogenic factors not only contribute to the maintenance of hypertension but may even be an initiating factor. The characteristic cerebral phenomena of hypertension and the effects of operations on the autonomic nervous system, as well as the effect of psychogenic factors on the clinical course, are offered in support of this view.

That essential hypertension in man, including the malignant variety, has the same essential pathogenesis as experimental hypertension is also indicated by the fact that in both conditions the blood pressure, as well as the clinical symptoms, has been relieved by the administration of the antipressor substance which Page and his co-workers and Harrison and associates have discovered.

This view is further strengthened by the experimental injection and infusion of angiotonin into the veins of human subjects.[108] The rises in blood pressure which followed this procedure were characteristic of clinical hypertension, as well as of experimental hypertension in animals.

It seems probable that persistent hypertension may result from, or at least be associated with, the paroxysmal hypertension caused by a pheochromocytoma of an adrenal gland. Several cases of paroxysmal hypertension have been reported, and emphasis has been placed on

108. Corcoran, A. C.; Kohlstaedt, K. G., and Page, I. H.: Changes of Arterial Blood Pressure and Renal Hemodynamics by Injection of Angiotonin in Human Beings, Proc. Soc. Exper. Biol. & Med. **46**:244 (Feb.) 1941.

the importance of diagnosis, because if this disorder is recognized sufficiently early surgical removal of the tumor may result in complete cure.

Van Epps, Hyndman and Greene [109] comment particularly on the symptomatology. A history of paroxysmal attacks of peculiar sensations may be the only subjective manifestation. The sensations may be located in the neck, the epigastrium or the substernal region. The sensation may be one of fulness, swelling, choking or pressure in the chest suggesting angina pectoris. Pain in the epigastrium, such as sometimes occurs in cases of peptic ulcer, may be the outstanding symptom. Angiospasm of the extremities or the tip of the nose is also described. Some of the other characteristic symptoms are a rise in both systolic and diastolic pressures, pallor, tremor, headache, vertigo and cardiac palpitation. The duration of paroxysms may vary from a few minutes to forty-eight hours.

Brunschwig and Humphreys [110] emphasize the presence of syncope, an increase of 100 mm. in the systolic pressure and a marked rise in the diastolic pressure. It has been assumed that the attacks are due to the liberation of epinephrine or epinephrine-like substances from the tumor. The attack seems to be often initiated by trauma, by motion in a certain direction, such as bending or stooping, or even by emotional strain.

Attempts to visualize the tumor, even by means of the perirenal insufflation of air or oxygen, often fail. If such a measure is attempted, it would appear that oxygen is much the safer substance to employ. Considerable difficulty and even dangerous symptoms have resulted from the use of air. In 1 case reported by Brunschwig and Humphreys no actual tumor involving an adrenal gland was found, although the symptoms were typical. In such a case it is possible that a tumor arising from a secondary adrenal rest in any of various locations might be responsible. Under such circumstances location of the tumor would be exceedingly difficult.

Confirming results of previous similar studies, Odel [111] states that malignant hypertension must be regarded as a diffuse arteriolar disease and that no organ can escape the effects of the rise in blood

109. Van Epps, E. F.; Hyndman, O. R., and Greene, J. A.: Clinical Manifestations of Paroxysmal Hypertension Associated with Pheochromocytoma of Adrenal, Arch. Int. Med. **65**:1123 (June) 1940.

110. Brunschwig, A., and Humphreys, E.: Excision of Pheochromocytoma Following Near Fatal Attack of Paroxysmal Hypertension, J. A. M. A. **115**:355 (Aug. 3) 1940.

111. Odel, H. M.: Structural Changes in the Arterioles of the Myocardium in Diffuse Arteriolar Disease with Hypertension on Group Four, Arch. Int. Med. **66**:479 (Sept.) 1940.

pressure. Structural changes in the arterioles have been demonstrated, particularly in the brain, kidneys and myocardium. Odel found that structural changes in the arterioles of the heart apparently do not progress at the same rate or to the same degree as do similar changes elsewhere in the body. Change was observed primarily in the arterioles of the myocardium. The nature, and even the degree, of alteration in these structures varied widely. Increase in the nuclei of the media seems to occur early. Hyperplasia of the internal elastic layer, proliferation of the intima and degenerative changes follow much later. In some instances no arteriolar change was noted, even though it was relatively marked in other organs.

Both the pathogenesis and the experimental study of renal hypertension have been considered in a review by McCann.[112] He has included the essential reports on the presence of pressor substances arising from renal ischemia, as well as on the presence and defects of a depressor substance. He has also discussed clinical hypertension from the standpoint of urologic diseases. This phase of the problem is therefore not included in this review.

HYPOTENSION

Stead and Ebert [113] describe postural hypotension as a disease of the sympathetic nervous system. Three cases of the typical form were carefully studied. Syncope, weakness, loss of consciousness and vertigo in the upright position or after exercise were the outstanding symptoms. Sometimes rather vigorous exercise seemed to be necessary to induce an episode. One man was unable to shave while standing because of tremor and ataxia. In a standing position his arterial pressure fell to 58 mm. or lower in the systolic phase. In a horizontal position the blood pressure of another patient averaged 90 systolic and 60 diastolic in the morning, while in the afternoon it was always higher, averaging 160 systolic and 95 diastolic. In the upright position the pressure dropped to 50 mm. or lower, while the heart rate increased 30 to 40 beats per minute. This variation of pressure at different times of the day was noted in 2 of the 3 cases. It is interesting that no signs or symptoms of impaired cerebral function occurred unless the pressure fell to 50 mm. of mercury systolic or less. The initial symptoms were pallor, blurring of vision, tremor of the hands and inability to understand commands. Clonic movement of the arms and legs occurred. There was no recollection of the events which took place during such an

112. McCann, W. S.: Bright's Disease: A Review of the Recent Literature, Arch. Int. Med. **67**:680 (March) 1941.

113. Stead, E. A., and Ebert, R. V.: Postural Hypotension: A Disease of the Sympathetic Nervous System, Arch. Int. Med. **67**:547 (March) 1941.

episode. Nausea, sweating and slow pulse rate do not occur in this type of syncope, as they do in the ordinary type of fainting or in that associated with increased carotid sinus reflex irritability. The essential defect determined by the writers from their observations in these 3 cases was a failure of the normal response to change in posture. No more blood is pooled in the lower parts of the body on standing than there is in normal subjects under similar conditions. The pooling of the normal amount of blood causes an abnormal fall in blood pressure through the failure of the normal reflex. The location of the defect in the sympathetic nervous system is not apparent from these studies, although it would seem that whatever defect existed might involve the central portions of the sympathetic mechanism rather than peripheral elements of the reflex arc. If the lesions are extensive, other manifestations of loss of sympathetic function, such as disturbances in sweating, temperature of the body and heart rate, might be expected. In view of the evidence from these studies, it might well be supposed that postural hypotension would occur after extensive sympathectomy for the relief of hypertension. Although postural changes in pressure under similar conditions have been previously reported, the earlier descriptions of symptoms have not approached that presented by these authors.

A CRITICAL REVIEW OF THE SURGICAL TREATMENT

BY DR. DE TAKÁTS AND DR. JESSER

PARAVERTEBRAL BLOCK

Because of the widespread use of alcohol injections into the sympathetic trunk or ganglions, Merrick's [114] study of the degeneration and recovery of autonomic neurons following alcohol block deserves considerable interest. The author injected 95 per cent alcohol into cats, either by the customary paravertebral approach or directly into the ganglion or ramus. The changes which occur after infiltration of a ganglion differ from those which follow when the ramus is infiltrated. Injection into a ganglion produces a permanent block to all the postganglionic fibers taking origin from it, since the alcohol kills the ganglion cells. After thirty-five days nothing remains but a connective tissue scar. In order to obtain this result, however, the alcohol must be injected into the ganglion or in its close vicinity. When the ramus is infiltrated the alcohol dissolves the myelin sheath and interrupts the continuity of the axon, so that the distal segments undergo typical wallerian degeneration. Retrograde changes also occur in cell bodies

114. Merrick, R. L.: Degeneration and Recovery of Autonomic Neurons Following Alcoholic Block, Ann. Surg. **113**:298 (Feb.) 1941.

proximal to the injection. While the nerve elements may be completely destroyed, the fibrous elements of the ramus maintain its continuity. Blocking of this type is less permanent than that obtained by ramisection. The fibers penetrate the scar easily, and function is reestablished. Regeneration of myelin was apparent in ninety days. In one hundred and seventy days function was restored through a preganglionic fiber blocked with alcohol.

The author points out that permanent block of the sympathetic impulses to the abdominal viscera by means of such injections is impossible, since most of the neurons from which postganglionic fibers to these organs are derived are located in the prevertebral ganglions. On the other hand, permanent and complete block of sympathetic impulses to the thoracic viscera or the extremities may be produced by paravertebral injection, since infiltration of the ganglions destroys the cells of the postganglionic fibers.

This work explains why in certain cases alcohol block has only an evanescent effect, even though complete paralysis of the sympathetic nerves is obtained at the time of injection. It also indicates that surgical sympathectomy, whenever the patient's condition permits, is superior to chemical block, because regeneration can be more readily prevented and because postganglionic degeneration, with its undesirable phenomena, need not be produced.

Of 62 patients treated by White [115] with paravertebral injections of alcohol for angina pectoris, 52 per cent had complete or nearly complete relief from pain, while 30.5 per cent had reduction of severe attacks to a mild form, which could be treated satisfactorily by routine medication. An unsatisfactory result was obtained in 9.5 per cent, and 8 per cent died within two weeks of the injection. In the author's opinion, alcohol injections should be reserved exclusively for the patient with intolerable pain who is a poor operative risk. He describes the technic in detail.

Certainly no other method, such as total thyroidectomy, cardiomyopexy, omentopexy or cervicodorsal sympathectomy, can offer such results to the severely handicapped patient. Our method of choice for younger and not too severely handicapped patients is dorsal sympathectomy, but this operation cannot be carried out on the majority of patients. The complications of alcohol block, such as pleuritic pain, pneumothorax, intercostal neuritis and occasional coronary thrombosis, are offset by the spectacular relief from pain which occurs in half of the intractable cases.

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115. White, J. C.: Technique and Paravertebral Alcohol Injection: Methods and Safeguard in Its Use in the Treatment of Angina Pectoris, Surg., Gynec. & Obst. **71**:334 (Sept.) 1940.

The prevention of ischemic gangrene following occlusion of the major peripheral arteries by paravertebral block is stressed by Gage and Ochsner.[116] They employed the block of the sympathetic nerves as a preliminary procedure to the ligation of major arteries in 10 cases. In all but 2 cases the collateral circulation was found to be inadequate. In no case did gangrene set in after the main artery was tied. Acute arterial embolism was treated in the same manner in 4 additional cases. The authors state that sympathetic block successfully counteracts the perverted physiologic processes which occur when a major artery is occluded. It dilates the main and collateral vessels, raises the arterial and venous pressures, increases the flow of blood per minute through the main and collateral arteries and increases arteriolar pulsations and lymph flow. The size and number of the vasa vasorum are increased; collateral vessels develop more readily, and the blood supply of the muscles improves. All in all, it prevents ischemic gangrene. They favor repeated procaine block against permanent destruction of the sympathetic chain and ganglions.

Our experience with this method has been equally favorable. In the case of the handicapped patient who has just suffered acute arterial embolism after auricular fibrillation or mural thrombosis in the left side of the heart, the method is admirably suitable for the protection of the limb against gangrene. When deliberate ligation of major arteries is contemplated in a case of peripheral aneurysm, such as one of the iliofemoral or popliteal arteries, surgical sympathectomy, as advocated by Veal,[117] has yielded us excellent functional results.

VENOUS OCCLUSIONS

Glasser and Lesser[118] report 20 cases of severe organic arterial disease of the lower extremities in which arteriosclerosis was the predominant feature. Ligation of the femoral vein was performed in all cases. In 16 cases the relief of pain within twelve hours was dramatic. In 2 of 18 cases in which the pedal pulses were absent the pulses became palpable. In 10 of 17 cases in which gangrene was present definite demarcation, with spontaneous separation of the localized gangrene, was obtained. In 5 cases progressive spread of gangrene necessitated midthigh amputation.

116. Gage, J. M., and Ochsner, A.: The Prevention of Ischemic Gangrene Following Surgical Operations upon the Major Peripheral Arteries by Chemical Section of the Cervicodorsal and Lumbar Sympathetics, Ann. Surg. **112**:938 (Nov.) 1940.

117. Veal, J. R.: The Value of Sympathetic Interruption Following Surgical Repair of Peripheral Aneurysms, M. Ann. District of Columbia **9**:227 (July) 1940.

118. Glasser, S. T., and Lesser, A.: Femoral Vein Ligation for Chronic Arterial Diseases, Am. J. Surg. **52**:100 (April) 1941.

In previous reviews we have reported on attempts to improve circulation by ligation of concomitant veins. There is good experimental and clinical evidence that when a major artery is ligated the concomitant vein is advantageously tied. But in the case of chronic vascular occlusion the procedure is fraught with the danger of accelerating gangrene or stirring up infection. As a prophylactic measure against pulmonary embolism, however, Veal [119] has conclusively shown its value in amputations of the lower extremity.

In a thought-provoking article Homans [120] points to thrombosis of the deep veins of the lower leg as a source of pulmonary embolism. This type of thrombosis is difficult to identify, although lameness on walking up and down stairs, pain in the popliteal fossa on dorsiflexion of the foot, slight edema and cyanosis limited to the lower portion of the leg are highly suggestive. Conservative treatment is justified only until such signs and symptoms recur after immobilization. In the presence of a bland thrombus below the knee the common femoral vein is exposed, and if it is free of clots the superficial femoral vein may be tied. This will not lead to cyanosis or swelling of the leg. If a clot is found in the deep or the superficial femoral vein, it is sucked out, if possible, and the vein is tied or sutured. Heparinization of the patient follows. Ligature of the common femoral and the deep femoral vein produces permanent cyanosis and edema but may be a life-saving procedure. Sears [121] has also reported some instructive cases of ligation of the femoral vein.

The crux of the situation is an early and accurate diagnosis of the bland, nonadherent thrombus at or below the knee. In an important monograph Bauer [122] reports the results of venographic study of thromboembolic disease of the lower extremities. He believes that this process invariably starts in the deep veins of the lower portion of the leg. Its earlier stages can be unmasked by injecting contrast material into the short saphenous vein. If the deep veins of the lower part of the leg do not fill and yet the femoral vein is visualized, the foot of the bed is elevated and heparin is administered. If the femoral vein is also invisible, there are two possibilities. Tenderness over the femoral vein

119. Veal, J. R.: High Ligation of the Femoral Vein in Amputations of the Lower Extremities, J. A. M. A. **114**:1616 (April 27) 1940.

120. Homans, J.: Exploration and Division of the Femoral and Iliac Veins in the Treatment of Thrombophlebitis of the Leg, New England J. Med. **224**:179 (Jan. 30) 1941.

121. Sears, J. B.: Experience with Femoral Veins: Ligation for Prophylaxis of Postoperative Pulmonary Embolism, New England J. Med. **224**:108 (Jan. 16) 1941.

122. Bauer, G.: A Venographic Study of Thrombo-Embolic Problems, Acta chir. Scandinav. (supp. 61) **84**:1, 1941.

and swelling of the thigh are signs of an adherent thrombus. Heparin will be useful only in preventing propagation of this thrombus or in preventing thrombus formation in the veins of the muscles of the other leg. If there is no tenderness over the femoral vein and yet roentgenograms reveal no filling, the risk of pulmonary embolism is great, because there is a bland, nonadherent, floating thrombus in the femoral vein. Elevation of the limb and energetic treatment with heparin are indicated; ligation of the vein is done in case an infarct has occurred. To determine the site of ligation the long saphenous vein is exposed and through it the iliofemoral segment is visualized. If the femoral vein is free, it is ligated below the vena profunda; if the deep femoral or the iliac vein is involved, a ligature of the vein has to be made above the thrombus.

One can readily object to such a simplification of a complicated and unpredictable course of events, but important lessons, which are corroborated by clinical experience, can be learned from this study. One is the frequency with which typical iliofemoral thrombosis actually starts in the muscles of the calf. This treacherous, often unrecognized, thrombosis, to which Homans first drew attention, was discussed in last year's review. Another lesson is the necessity of stressing the well known clinical fact that once a typical milk leg appears in the form of painful, deep thrombophlebitis in the groin, the danger of pulmonary embolism is slight. The real danger comes from the unrecognized floating thrombus in the femoral vein which is not tender to pressure and produces no edema; the condition can probably be most accurately diagnosed by venographic examination. Dougherty and Homans [123] have described a simple procedure.

Veal [124] gives an excellent description of a syndrome based on personal experience with 17 cases of axillary or subclavian venous thrombosis. The chief symptoms are pain in the arm and shoulder; massive pitting edema of the entire extremity; weakness and partial loss of function of the arm; preservation of the radial pulse; elevation of the systolic arterial pressure on the affected side; palpable, tender, cordlike swelling along the course of the brachial basilic or axillary veins; marked elevation of the local venous pressure, and decrease in the oxygen content of the venous blood of the affected arm. He emphasizes the post-thrombotic syndrome, the severity of which depends on the adequate development of collateral circulation. He believes that surgical procedures for this syndrome are not justified.

123. Dougherty, J., and Homans, J.: Venography: A Clinical Study, Surg., Gynec. & Obst. **71**:697 (Dec.) 1940.

124. Veal, J. R.: Thrombosis of the Axillary and Subclavian Veins with a Note on the Post-Thrombotic Syndrome, Am. J. M. Sc. **200**:27 (July) 1940.

In our experience the early forms of the condition respond well to repeated procaine blocks of the stellate ganglion; in the late forms resection of the thrombosed venous segment, which serves as a focus of irritation for vasomotor reflexes, has been worth while.

ARTERIAL OCCLUSIONS

Pearse [125] reviews in detail the various methods used for gradual occlusion of large arteries. After many trials on dogs he found that cellophane wrapped loosely around large arteries, such as the thoracic aorta or the carotid arteries, had an irritant quality which caused a steadily progressive constriction of the vessel, and even obliteration in some instances. The constriction may become so tight that it results in rupture of the aorta. The only drawback of the method is the intensity of the reaction caused by the cellophane.

The clinical implications of such aseptic, gradual occlusions are obvious. Thus such arteries as the carotids or the aortic bifurcation, the sudden closure of which may be disastrous, could be gradually occluded by placing a graded amount of tissue irritant around them. No clinical report has become available so far, but the use of this procedure seems promising.

Murray and Janes [126] report an interesting set of experiments in preventing failure of circulation following injuries to large arteries. They inserted glass cannulas between the cut ends of the common carotid arteries of dogs and secured them by tying a linen ligature around the cut ends of the vessels and the cannulas. Without the use of heparin the tubes became plugged in twenty minutes, but heparin kept the cannulas patent by raising the clotting time to thirteen minutes and more.

Consideration of the experimental evidence suggests that it might be possible to insert a glass cannula into a torn artery soon after an accident. With suitable hourly injections of heparin the cannula could be kept patent until the injured person could be removed to a hospital for final repair of the vessel.

Smith [127] described a new technic for simplifying vascular anastomoses, in which a soluble rod made of dextrose and coated with an oily lubricant (such as a mixture of theobroma oil U. S. P. [cocoa butter] and paraffin) is introduced into the vessel. This mechanical form facilitates the proper approximation and suture of the ends of the

125. Pearse, H. E.: Experimental Studies in the Occlusion of Large Arteries, Ann. Surg. **112**:934 (Nov.) 1940.

126. Murray, G., and Janes, J. M.: Prevention of Acute Failure of Circulation Following Injuries to Large Arteries: Experiments with Glass Cannulae Kept Patent by Administration of Heparin, Brit. M. J. **2**:6 (July 6) 1940.

127. Smith S.: A Soluble Rod as an Aid to Vascular Anastomosis: An Experimental Study, Arch. Surg. **41**:1004 (Oct.) 1940.

vessel, just as a wooden egg aids in the mending of a stocking. The soluble rod dissolves in the blood stream within a minute after the circulation is released.

Linton [128] emphasizes the great importance of thrombosis occurring distal to the embolic occlusion of major arteries. The most common cause of gangrene following peripheral embolism is failure to institute adequate treatment before the arteries distal to the embolus have been irreparably damaged. Marked peripheral vasoconstriction of the arteries distal to the site of occlusion uniformly occurs soon after the lodgment of the embolus. The artery proximal to the embolus is not affected to the same degree. The restoration of the circulation following peripheral embolism can be brought about by early adequate treatment, possibly within the first six hours. The place and value of embolectomy, intermittent venous congestion, paravertebral sympathetic block and heparin are discussed. The article is strongly recommended to all internists dealing with cardiovascular emergencies.

Peripheral arterial embolism as seen and treated at the Cook County Hospital, in Chicago, is discussed by Koucky, Beck and Hoffman,[49] who give a true picture not of the ideal procedure but of what is actually happening in large charity hospitals throughout the country, with the majority of physicians still not alert to the grave implications of acute vascular occlusion. They emphasize the proper time of amputation when embolectomy has failed or is deemed not indicated and warn of waiting too long when toxemia is evident. The use of heparin as a valuable adjunct in cases of arterial suture, arteriovenous fistula, venous grafts and arterial embolism is again discussed by Murray.[129] One hundred and twenty-five patients with thrombophlebitis, phlebothrombosis and pulmonary embolism were treated, with marked success. Of 46 patients with pulmonary embolism, only 2 had further small emboli, even though heparin has no effect on existing thrombi.

It seems to us that heparin is clearly indicated now after arterial or venous suture or in cases of pulmonary embolism. As a preventive measure its use seems justified only in the "endangered" group, that is, elderly patients who have had an attack of venous thrombosis or pulmonary infarct.

Crafoord and Jorpes [130] treated 325 patients with injections of heparin postoperatively. Not a single thromboembolic episode occurred. Of a control series of 1,111 patients with a similar condition, this

128. Linton, R. R.: Peripheral Arterial Embolism, New England J. Med. **224**: 189 (Jan. 30) 1941.

129. Murray, G.: Heparin in Thrombosis and Blood Vessel Surgery, Surg., Gynec. & Obst. **72**:340 (Feb., no. 2 A) 1941.

130. Crafoord, C., and Jorpes, E.: Heparin as a Prophylactic Against Thrombosis, J. A. M. A. **116**:2831 (June 28) 1941.

complication occurred in 9 per cent. In both series the patients selected were over 35 years of age and had been subjected to operations on the gastrointestinal tract, the biliary system or the urinary passages or to major operations for hernia or varices. Heparin was given intermittently in intravenous injections four times a day. The treatment was continued for five to ten days.

We have tried both the continuous and the intermittent administration of heparin. Certainly the patient is far more comfortable if the continuous intravenous drip is avoided. Not enough is known, however, about the dangers of the marked fluctuations of coagulation time which follow single intravenous injections of heparin.

Repeated removal of emboli, caused in 1 case by a sarcoma dislodged from the pulmonary veins [131] and in another by a fibrillating heart,[132] brought about permanent restoration of circulation in seemingly hopeless cases. In both instances the embolectomies were aided by the use of heparin.

The mechanical and vasomotor effects of an arterial ligature are analyzed by Leriche and Werquin.[133] The ligature acts as a severe trauma and produces reflex vasoconstriction distally. This reflex may be removed by resection of the obliterated length of the affected artery. They prove with arteriograms that when the collateral way is clear and thrombosis is not too extensive the artery becomes filled with opaque substance below the occlusion. When healthy muscles are present near the ligated artery and run parallel to the obstructed vessel the anastomotic arteriolar circulation is of great value. Ligature is dangerous when the neighboring muscles have a divergent pattern and no vascular anastomoses exist between them. The prophylactic measures against gangrene, ischemic sclerosis, claudication and trophic disturbances following ligature of major arteries are listed as (1) the use of suture instead of ligature whenever possible, (2) limited resection of the artery between two ligatures, (3) periarterial sympathectomy above the ligature and (4) infiltration or section of the regional portion of the sympathetic trunk and ganglions.

The article is an excellent summary of Leriche's many years of investigation in this field. Traumatic and military surgeons will derive a great deal of information from its study.

Leriche [46] describes the syndrome of terminal aortic occlusion by arteritis, characterized by sexual impotence in the male, weakness and

131. Groth, K. E.: Tumor Embolism of the Common Femoral Artery Treated by Embolectomy and Heparin, Surgery **8**:617 (Oct.) 1940.

132. MacFarlane, J. A.: Multiple Emboli Treated Surgically, Brit. M. J. **1**:971 (June 15) 1940.

133. Leriche, R., and Werquin, M. G.: Effects of Surgery on the Vasomotor System, Lancet **2**:296 (Sept. 7) 1940.

fatigue of the lower extremities, muscular atrophy and pallor of both limbs. There are no pulsations in either groin, but there is increased pressure in the upper extremities. As the condition advances the legs become cyanotic and desquamation of the skin develops, with small ulcerations. In 5 cases the first lumbar sympathetic ganglion was removed bilaterally; in 1 case resection of the thrombosed segment of the aorta and the iliac arteries was done in addition to sympathectomy. This seemed more beneficial than sympathectomy alone.

It is difficult to evaluate this procedure as the period of follow-up is short and the clinical data are meager. As usual, Leriche has a stimulating idea, which others might place on a more sound basis.

ANEURYSMS

In a symposium of the American Surgical Association the surgical treatment of aneurysm of the abdominal aorta was discussed by Matas, Bigger and Elkin. Matas [134] described the successful cure of an aneurysm of the abdominal aorta which he brought about in 1923. The patient died of tuberculosis more than one year after the operation. At autopsy it was demonstrated that collateral circulation above and below the aneurysm was well established. The clinical evidence of cure was confirmed by complete consolidation of the contents of the sac. The cotton tape ligatures employed in this case were well tolerated by the tissues. They caused a total aortic occlusion for the first nine days after the operation, after which they yielded slightly. Nevertheless, the sac filled with a clot because of the marked reduction of the aortic stream.

Bigger [135] collected the cases of ligation of the abdominal aorta previously reported in the literature and added 2 others. In the first case, the patient was a poor surgical risk; cardiac failure developed, and death followed occlusion of the aorta proximal to the aneurysm. In the second case, the patient was a young man whose ruptured traumatic aneurysm was treated by preliminary occlusion of the aorta proximal to the sac. A month later a restorative endoaneurysmorrhaphy was done. A year after this operation the patient appeared to be well; there was no evidence of the aneurysm, and the lumen of the aorta was obviously patent.

Elkin,[136] after reviewing the literature, reports the proximal ligation of a large pulsating aneurysm situated just below the origin of the inferior mesenteric artery. Two cotton tapes were tied around the aorta

134. Matas, R.: Aneurysm of the Abdominal Aorta at Its Bifurcation into the Common Iliac Arteries, Ann. Surg. **112**:909 (Nov.) 1940.

135. Bigger, J. A.: The Surgical Treatment of Aneurysm of the Abdominal Aorta, Ann. Surg. **112**:879 (Nov.) 1940.

136. Elkin, D. C.: Aneurysm of the Abdominal Aorta, Ann. Surg. **112**:895 (Nov.) 1940.

until the pulsation of the femoral vessels could hardly be felt. Since there was no increased vascularity about the aneurysm, it was thought best to produce a partial occlusion. Eleven months later there was a slight pulsation in the mass. The patient had resumed his ministerial duties and was driving his car.

Elkin discusses certain inherent difficulties in ligation of the aorta, aside from the technical performance. First of all, the location of the aneurysm is rarely at a point where proximal ligation can be undertaken without menace to the vitality of the kidneys or intestine. The most frequent site is in the region of the celiac axis, and partial distal ligation, which is not an especially successful procedure, is the only possibility. Only rarely is an unruptured aneurysm found at the iliac bifurcation and in such a position that the aorta can be occluded distal to the inferior mesenteric artery. Complete ligation above that vessel would very likely result in gangrene of the sigmoid flexure of the colon.

An efficient collateral circulation rarely exists about an aortic aneurysm, and gangrene of the extremities will result if the vessel is occluded. But if the collateral circulation is efficient, vessels may reenter the aneurysmal sac and cause an early recurrence.

The type of ligature and the manner of occlusion still remain an unsolved problem. Possibly the method of Pearse, with the cellophane reenforced by partial tape ligatures or sclerosing solutions between partial ligatures, may offer a solution.

The effect of aortic ligation on the heart has been a subject of much dispute and is still unsettled. Failure of the left side of the heart occurred in some patients soon after ligation.

It seems to us that with an earlier diagnosis and the use of the principle of gradual occlusion an occasional patient might be restored to economic efficiency. This has certainly been true of patients with wired aneurysms of the thoracic aorta.

Holman [137] reviews a group of 21 cases of arteriovenous fistula and adds interesting experimental observations which tend to show that after the establishment of a large arteriovenous fistula the heart first diminishes in size and then gradually dilates. The dilatation is not restricted to the heart but affects all the vessels involved in the fistulous circuit. When dilatation of the heart outstrips hypertrophy, decompensation occurs; when dilatation is paralleled by a commensurate hypertrophy, great enlargement and dilatation of the heart may occur without decompensation. The physiologic effect of the fistula depends on the volume of blood diverted through the fistula and therefore on its size.

The transient high systolic and diastolic pressures that persist for several days after operative closure of the fistula are due to the increase

137. Holman, E.: Clinical and Experimental Observations on Arteriovenous Fistulae, Ann. Surg. **112**:840 (Nov.) 1940.

in blood volume that has occurred during the existence of the fistula. The permanent elevation of diastolic pressure is secondary to the elimination of an area of decreased peripheral resistance.

The author shows on the basis of detailed case reports that complete cardiac decompensation, with peripheral edema, ascites, hydrothorax and extreme dilatation of the heart, may be corrected, with return of the heart to its normal size after closure of the fistula. An increase in blood pressure and a fall in pulse rate occurring on digital closure of the fistula indicate that the fistula is large, that it will not close spontaneously and that it will almost certainly produce deleterious effects on the circulation. The increase in blood pressure and fall in pulse rate are the first evidence that the circulatory bed is beginning to dilate, even though such dilatation may not be detectable by the usual means. The extent of the increase in blood pressure and fall in pulse rate depends on the duration of the fistula. It is greatest in the fistulas of long duration, with great cardiac dilatation.

A temporary but great increase in blood pressure and fall in pulse rate may occur immediately after the surgical closure of the fistula. These changes are due to a great increase in blood volume, which is an inevitable accompaniment of a large fistula of long duration. The increased blood volume is reduced immediately after the operation, but transient overdistention of an already dilated heart may occur because of the redistribution of the formerly diverted blood into its normal channels.

Whether the increased blood volume is responsible for the cardiac dilatation or whether, as Reid [138] has suggested, the increase in blood volume is connected with the impending cardiac failure is a debated question. It is certain that we have repeatedly amazed our medical colleagues by demonstrating to them the rapid decrease of the size of the heart to normal following the operative closure of a fistula.

Lee and Freeman [139] reported 3 cases in which angioma of the lower extremity was fed from the venous side through back pressure on standing instead of from the arterial side, as in the more common type of congenital arteriovenous aneurysm. That filling occurred from the venous side was proved by lack of pulsation of the veins, absence of increase in the oxygen saturation of the venous blood taken from the affected extremities and prevention of filling by the application of a venous tourniquet.

The treatment suggested is a ligation of the veins with incompetent valves, with subsequent sclerosis of the remaining segment if necessary.

138. Reid, M. R., in discussion on Holman.[107]

139. Lee, W. E., and Freeman, N. E.: Circulatory Disturbances Produced by Extensive Angiomata of the Lower Extremities Associated with Varicose Veins, Ann. Surg. **112**:960 (Nov.) 1940.

In the cases reported the ligation of the incompetent veins not only reduced the size of the angioma but relieved the marked postural hypotension, which was severe enough to cause fainting. In 1 patient the increase in volume of the lower portion of the leg when the erect posture was assumed was 475 cc.

This postural hypotension due to defective venous valves and consecutive "bleeding" into the affected extremity is not infrequent in cases of extensive varicose veins. In cases of congenital venous aneurysm the capacity of the venous bed is even greater. The syndrome should be emphasized, as it may be confused with the carotid sinus syndrome.

Cases of arteriovenous fistula of the limb are described by Lewis [140] in which the circulation of the distal part of the limb becomes restored to, or actually beyond, normal over a period of years. Such restoration may be due in part to decreased vasomotor tone, but may result also from vascular growth. The latter may be controlled by a chemical stimulant arising locally as a product of the need of the tissues and acting locally.

This report touches on an important surgical problem. The surgeon usually likes to wait six months or longer after the development of an arteriovenous fistula before he attempts repair. On the other hand, a large fistula throws such a burden on the heart that waiting too long may bring about irreversible damage. The suggestion of Gage and Ochsner and Veal to increase collateral circulation in the affected limb by a preliminary sympathectomy is germane to this discussion. While Lewis' presentation, as always, is concise, simple and logical, his hypothesis is not supported by observations on simple arterial aneurysm, associated with which there is often great need for blood and vascular growth and in which collateral circulation is notoriously poor. The diversion of blood into the venous channels, the high oxygen saturation of the venous capillary blood and its more facile diffusion into the tissues must be responsible for the more rapid growth of vascular tissue in arteriovenous fistulas; as a matter of fact, bone grows faster and the entire limb gets larger in patients whose epiphyses are not yet closed.

THE CAROTID SINUS SYNDROME

Mulholland and Rovenstine [141] review the diagnosis, surgical procedure and preoperative and postoperative care in 5 cases of carotid sinus syndrome. In all 5 cases diagnosis was made by digital pressure over

140. Lewis, T.: The Adjustment of Blood Flow to the Affected Limb in Arteriovenous Fistula, Clin. Sc. **4**:277 (Oct.) 1940.

141. Mulholland, J. H., and Rovenstine, E. A.: Surgery in the Carotid Sinus Syndrome, Surgery **9**:751 (May) 1941.

the bifurcation of the common carotid artery at the level of the upper border of the thyroid cartilage. The pulse rate, blood pressure and electrocardiographic changes were determined during the manipulation. The patients were classified into vagal, pressor and cerebral types. When the carotid sinus nerve was blocked with procaine, pressure over the carotid bulb should have given no symptoms.

It is striking that the patients were all about or over 60 years of age and might have had disturbances of the cerebral or cardiac circulation. It may well be that the exaggerated reflex phenomena were not due to an increasingly sensitive carotid sinus, but that the cerebral reflex arc or the end organs in the cardiac muscle were hyperreactive. When this is the case the sensitive carotid sinus plays a minor part in the disturbed reflex. Further studies on this interesting surgical problem are indicated.

CERVICAL RIB AND THE SCALENUS SYNDROME

Jelsma [142] considers the history and symptoms of the scalenus syndrome; of 45 patients operated on, 26 had complete relief of pain one month after operation and 7 received satisfactory, but not complete, relief. Two obtained 50 per cent relief. The operations consisted of section of the muscles or neurolysis or both.

Kaplan [143] analyzed the relation of the scalenus anticus muscle to pain in the shoulder. He emphasized the diagnostic significance of infiltrating the lateral margin of the muscle with solution of procaine hydrochloride to determine the influence of relaxing this muscle on the symptoms accompanying painful lesions of the shoulder. Among the conditions studied were the scalenus syndrome (16 cases, in 6 of which the condition followed trauma), subacromial bursitis with adhesions (12 cases) and lesions of miscellaneous origin (3 cases). The author believes that such lesions produce a secondary spasm of the scalenus muscle.

This analysis is timely, as it points to the importance of making an accurate diagnosis of the scalenus syndrome before section of the muscle is undertaken. While the operation is remarkably successful in the properly selected case, many patients undergo unnecessary operations without relief. In our experience subacromial bursitis, osteoarthritis of the cervical portion of the spine and early degenerative lesions of the spinal cord must be carefully eliminated before scalenotomy is advised. Kaplan reports striking results from repeated injections of procaine hydrochloride into the muscle.

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142. Jelsma, F.: Scalenus Anticus Syndrome: End Results of One Hundred and Fifteen Cases, Internat. Clin. **4**:219 (Dec.) 1940.

143. Kaplan, C.: Relation of the Scalenus Anticus Muscle to Pain in the Shoulder, Arch. Surg. **42**:739 (April) 1941.

SYMPATHECTOMY IN TREATMENT OF PERIPHERAL CIRCULATORY DISTURBANCES

In spite of many hundreds of operations on the sympathetic nervous system, surgeons had to base their scheme of the outflow of preganglionic fibers from the cord to the limbs on the early experiments of Langley, Bayliss and Bradford, who used erection of hairs, sweating or vascular changes for recording sympathetic activity. Furthermore, the experiments were carried out on cats and dogs, which possess thirteen thoracic and seven lumbar spinal nerves. Sheehan and Marrazzi [144] utilized rhesus monkeys because they possess twelve thoracic nerves, as does man. Thus, whereas seven spinal roots participated in the preganglionic outflow to the lower extremity of the cat, only four roots contributed in the monkey—the twelfth thoracic to the third lumbar root, inclusive. In the upper limb of monkeys the outflow of preganglionic sympathetic fibers was confined to from the fourth to the eighth thoracic root, inclusive, with the major outflow occurring from the fifth, sixth and seventh thoracic spinal nerve roots.

Experiments on monkeys designed to study pathways of the sympathetic nervous system are gaining in importance; much previous knowledge, based on experiments with cats and dogs, will have to be revised.

During the past five years, Smithwick [145] has done 115 preganglionic sympathectomies for the upper extremity in cases of vascular spasm. He found that the upper extremity can be thoroughly sympathectomized by interrupting the outflow from the second and third dorsal segments and dividing the sympathetic trunk below the third dorsal ganglion. The outflow from the first dorsal segment is thus left intact. While the immediate results were satisfactory, the late results were variable, due mostly to regeneration of sympathetic motor fibers. A number of variations in surgical technic were tried to check regeneration. Finally, the anterior roots of the second and third dorsal spinal nerves were sectioned intraspinally, which leaves them in a water-tight compartment when the meninges heal. To prevent regeneration toward the decentralized second and third ganglions, these were wrapped in a small silk cylinder and the distal end of the trunk was ligated. Early results with this method have been excellent. Late results cannot yet be reported.

Smithwick feels that the immediate and early results of preganglionic denervation of the upper extremity are uniformly satisfactory. Here

144. Sheehan, D., and Marrazzi, A. S., Jr.: Preganglionic Outflow to the Limbs of Monkeys, J. Neurophysiol. **4**:68 (Jan.) 1941.

145. Smithwick, R. H.: The Problem of Producing Complete and Lasting Denervation of the Upper Extremity by Preganglionic Section, Ann. Surg. **112**: 1085 (Dec.) 1940.

the degree of damage to tissue or local fault in the vessel wall is the limiting factor. If late results are not as satisfactory, this is due in the great majority of instances to regeneration. Therefore, the present surgical trend is to avoid or minimize this regeneration. He points out, however, that even if regeneration does take place, the patients are benefited by the operation. Their symptoms are milder and easier to control. The blood flow is well maintained from the shoulder to the mid-dorsum of the hand. The basal and middle portions of the fingers show an elevated temperature. The most marked change is in the finger tips. Regeneration is rarely complete, and the result is worth while from the patient's point of view.

Perhaps the best proof of Smithwick's contention that proper technic is of paramount importance in preventing regeneration is seen in the study of patients in whom one extremity remains dry, warm and free of spasm, whereas the other may show a small strip of moisture, cooling of the tips and recurrence of biphasic color changes. Yet both extremities have been denervated by the same technic in our clinics. One must assume with Smithwick that wide variations exist in the origin of preganglionic pathways; certainly, the disease is the same in the two extremities, and the recurrence is not due to failure of sympathectomy to influence vasospastic vascular disease.

After studying 22 patients exhibiting Raynaud's phenomena, Johnson [69] concurs with Hutchinson's conclusion that Raynaud's disease is not a clinical entity and that the peripheral manifestations observed are merely symptoms of some more fundamental disease. This is also in accord with the views of Hunt, which were discussed in our review of 1937. Hunt expressed the belief that Raynaud's disease is rare and that the Raynaud phenomenon occurs in a wide variety of definite and indefinite disorders. Patients who exhibit Raynaud's phenomena but who have a well recognizable cause for it should obviously be treated for the underlying condition. Johnson's attitude toward sympathectomy for Raynaud's disease is that the operation has been a complete failure and that circulation returns to the preoperative level in a short time, together with the symptoms. He presents 5 case reports in support of this statement. He feels that in all cases the patient's circulation returned to the preoperative level, because (1) the finger plethysmograph, while showing increased pulse waves shortly after sympathectomy, showed tracings similar to the preoperative ones, (2) local application of heat produced approximately the same amount of vasodilatation before as after sympathectomy, (3) median nerve block showed varying and not readily explainable responses in the anesthetized and unanesthetized fingers and (4) the symptoms recurred rather early in most cases.

These statements are so challenging and are based on such a thorough and panistaking study that their critical analysis is worth

while. In the first place, the value of the finger plethysmograph as an instrument of measuring blood flow to the finger may be seriously questioned. The plethysmograph, as has been repeatedly pointed out, measures the amplitude of the pulse volume; it registers the rapid systolic foward flow, but not the smaller systolic back flow or the slow forward diastolic flow. The net arterial inflow depends not only on the first and third phase but on the amount of the second phase, which has to be subtracted. Nor does the plethysmograph measure the circulation time through the extremity, which is decreased after sympathectomy. Obviously, when blood flow is more rapid more blood can pass through a given part. When the rate of blood flow was studied it was found to range from 0.02 cc. per minute per 10 cc. of tissue when the vessels were constricted to 12 cc. when they were dilated as much as a hundred times; certainly the plethysmograph is not an accurate means of measuring the state of circulation through the fingers.

That local application of heat produces vasodilatation after sympathectomy is well known; the capacity of smooth muscle to relax on direct application of heat is maintained. If the author had studied the effect of indirect reflex heat on sympathectomized fingers he would have found, provided the sympathectomy was complete, that the reflex heat does not produce vasodilatation in sympathectomized fingers. This was demonstrated first by Lewis. The observations on the effect of median nerve block are confusing. In 1 case the nerve block resulted in increased oscillations before, but not after, sympathectomy. In another case the median nerve block produced marked increase in pulsations after sympathectomy in the three fingers innervated by the median nerve, in spite of absence of sweating. One patient became emotionally unstable; I felt faint. Certainly a median nerve block which fails to produce increased oscillations in the fingers either means severe organic damage or partial paralysis with stimulation of the vasoconstrictors. The phenomenon of cooling and diminished pulsations in the nonanesthetized fingers occurring in the author's cases after median nerve block can be explained by the painful stimulus of the injection, which produces vasoconstriction in the nonanesthetized fingers, but is unable to act on the fingers in which the vasoconstrictor fibers are blocked by procaine hydrochloride. On the basis of these findings, Johnson promulgates the startling hypothesis that Raynaud's phenomena are brought about by diversion of blood from the fifth finger and are not due to active vasoconstriction. Nothing but his misinterpreted findings supports his assumption.

Study of the cases of the surgically treated patients reveals that 2 patients were operated on when indications were doubtful: 1 for rheumatoid arthritis and 1 for syphilitic endarteritis. If these 2 patients

did not show clinical improvement the fault may lie in their selection. One patient had hysterical attacks, which sometimes lasted an hour, and the symptoms recurred eight days after operation. In 1 patient with bilateral removal of the stellate and third dorsal ganglion—the second is not mentioned—median nerve block released a vasospasm, which is a definite proof of regeneration of fibers or an incomplete operation. In another patient after both lumbar sympathectomy and bilateral preganglionic dorsal sympathectomy the sweating function in the arms and hands had returned in about six days. The fifth patient had a postganglionic sympathectomy on one side and a preganglionic sympathectomy on the other. The effects of direct heat and median nerve block were the same before and after the operation; no mention was made of the clinical result.

On the basis of these 5 cases in which surgical procedures were done the author concludes that surgical treatment of the sympathetic nervous system is a therapeutic failure. It should be pointed out that some of these operations were incomplete, as either sweating or vasodilatation to nerve block was demonstrated. In a case of preganglionic sympathectomy the vasomotor paralysis was so transitory that it did not last longer than the traumatic effects of the operation. The procedure used could hardly have been the one which White and Smithwick have gradually developed.

The difference of opinion expressed by these two articles by Smithwick and Johnson is not as great as it would seem. That secondary types of vasospasm simulating Raynaud's disease should be analyzed and treated on an etiologic basis requires repeated emphasis. Suitable methods of analysis undertaken on patients suffering from Raynaud's disease and subjected to adequate preganglionic procedures, which show absence of sweating and no or small rises of temperature after somatic nerve block, yield information which is contrary to Johnson's pessimistic view of the value of surgical treatment of the sympathetic nerves in cases of vasospastic disease. These methods have been reviewed in previous years. Johnson's report will undoubtedly stimulate the publication of carefully followed surgical cases.

The post-traumatic circulatory and trophic disturbances, which are receiving increasing attention in industrial surgery and in treatment of war wounds, are represented by two excellent articles. Herrmann and Caldwell [146] believe that such disturbances should be recognized early. In the acute phase periarterial sympathectomy brings about a quick response and the undesirable sequelae are prevented. When the acute phase is missed the circulatory and trophic changes run their

146. Herrmann, L. G., and Caldwell, J. A.: Diagnosis and Treatment of Post-Traumatic Osteoporosis, Am. J. Surg. **51**:630 (March) 1941.

own slow, and sometimes irreversible, course. In the discussion of this paper Herrmann does not recommend ganglionectomy for this condition.

Homans [147] described interesting cases of minor causalgia following injuries and wounds. He considers sympathetic block is the treatment of choice but states that periarterial sympathectomy or ganglionectomy may have to be done in cases of the severe form. There is little hysterical element in this disease; yet most cases are first regarded and handled as instances of hysteria.

SURGICAL TREATMENT OF HYPERTENSION

There is continued interest in the surgical treatment of hypertension, because rest, sedatives, toxic depressants and psychoanalytic sessions, while of unquestionable temporary, palliative value, have failed to cure or arrest the progress of this disease. Hypertension with its sequelae is responsible for more than half a million deaths annually in the United States.

Peet, Woods and Braden [148] report on 350 patients who have had bilateral supradiaphragmatic splanchnic nerve sections and lower dorsal ganglionectomies. The authors prefer to operate only on patients less than 50 years of age with a systolic blood pressure over 200 mm. of mercury, an ability to concentrate the urine to a minimum specific gravity of 1.021 and a nonprotein nitrogen level of less than 45 mg. per hundred cubic centimeters of blood. In the analysis of results, 86.6 per cent of the patients had postoperative relief of major symptoms, especially headache; 81.3 per cent had improvement or complete relief from incapacitation; 51.4 per cent had a significant reduction of blood pressure, and 11.7 per cent had a return of blood pressure to normal. Improvement in retinal findings was conspicuous in that papilledema disappeared in 73.8 per cent of patients and exhibited some improvement in 69.4 per cent. Cardiac improvement was manifested by a better electrocardiographic tracing in 53.4 per cent and diminution of the size of the heart in 64 per cent. The urea clearance improved in 52.2 per cent of the patients and the urine concentration in 44.8 per per cent. In addition, the statement was made that the prognosis was better for women than for men, that the most favorable results were obtained in the age group below 30 and that the surgical mortality was

147. Homans, J.: Minor Causalgia Following Injuries and Wounds, Ann. Surg. **113**:932 (June) 1941.

148. Peet, M. M.; Woods, W. W., and Braden, S.: Surgical Treatment of Hypertension: Results in Three Hundred and Fifty Consecutive Cases Treated by Bilateral Supradiaphragmatic Splanchnicectomy and Lower Dorsal Sympathetic Ganglionectomy, J. A. M. A. **115**:1875 (Nov. 30) 1940.

3.4 per cent. The authors feel that their method offers the most hopeful approach among all surgical procedures.

It is interesting that in another larger series, that of Allen and Adson,[149] who report on 224 patients, the incidence of symptomatic relief and of lowering of blood pressure is approximately the same as that in the series just cited, although they employ a subdiaphragmatic splanchnic nerve section with partial resection of the celiac ganglion and also resect the upper two lumbar sympathetic ganglions. They state that while sympathectomy to produce permanent reduction of blood pressure is somewhat disappointing, the relief or amelioration of symptoms, with the extension of the expectancy of life for the patients in the advanced group, justifies the surgical procedure. In contradistinction to Peet and his co-workers, Allen and Adson feel that the results of operation for essential hypertension can be predicted with reasonable certainty by observing the response of the blood pressure to rest and sleep, to the ingestion of sodium amytal and to the intravenous injection of pentothal sodium. When poor results are predicted as a result of these responses the outcome is almost uniformly unfavorable. When good results are predicted some patients do not receive as much benefit from the operation as is anticipated.

Reports on a number of smaller series give essentially the same results as those of two large series just reviewed.[150] A courageous attempt to establish the value of and define the indications for surgical therapy is that of Rytand and Holman.[151] Using the supradiaphragmatic approach, they operated on 40 patients of all ages, with congestive heart failure, outright coronary occlusion, hemiplegia and glomerulonephritis. The patients who had the most severe renal and retinal lesions fared worst; those with minimal or no renal or retinal lesions fared best. Of their series of 40 patients, only 6 could be seriously considered as having had their prognoses altered by the operation. Six more patients felt better, but their arterial pressures were not lowered. In 9 patients there was no change. Eleven died within one and one-half years, with their conditions unchanged; 8 died within two weeks of the operation, a surgical mortality of 20 per cent.

This article focuses interest on two factors which influence results of the surgical treatment. One is the grouping and selection of patients

149. Allen, E. V., and Adson, A. W.: Medical Versus Surgical Treatment of Hypertension, Ann. Int. Med. **14**:288 (Aug.) 1940.

150. Crane, W.: The Surgical Treatment of Essential Hypertension, West. J. Surg. **49**:88 (Feb.) 1941. Wertheimer, P.: La splanchnicectomie bilatérale susdiaphragmatique dans le traitement chirurgical de l'hypertension artérielle, Presse méd. **48**:689 (Sept. 4-7) 1940.

151. Rytand, D. A., and Holman, E.: Arterial Hypertension and Section of the Splanchnic Nerves, Arch. Int. Med. **67**:1 (Jan.) 1941.

for operation. The four groups of Wagener, Keith and Barker, who classified diffuse arteriolar disease into early, moderate, marked and malignant forms, have been of great importance in predicting results. Not only is such grading applied to the patients in the Mayo Clinic, but the patients of Smithwick and those recently reported by one of us (G. de T.) and two associates were also subjected to it.[152] The results to be expected are distinctly dependent on the stage of the disease in which the operation is undertaken. In fact, in a recent admirable statistical survey, Woods[153] has shown on the material of Peet and co-workers that life expectancy in the four groups is definitely prolonged after operation, as compared with the duration of life in the group reported by Wagener, Keith and Barker, in which no operation was performed. The importance of Keith's work, which originally met with so much opposition, is now becoming obvious to such surgical groups as originally had little use for it.

The surgical technic, as well as the stage of the disease, has an important bearing on results. Smithwick[154] describes an extended splanchnic nerve section which combines the advantages and eliminates the disadvantages of the two previous operations. It is a complete resection of the major splanchnic nerve, from the fifth dorsal root down to the celiac ganglion. In addition, the sympathetic ganglionated trunk is removed from the ninth dorsal ganglion to below the first, or occasionally the second, lumbar sympathetic ganglion. In order to obtain this exposure the diaphragm must be incised and resutured. The renal arteries, renal pelves, ureters and adrenal glands may be inspected and palpated. Smithwick, in a preliminary report, discussed patients operated on by this method and pointed to the marked postural hypotension which must accompany this operation before the splanchnic denervation can be called complete. It is our belief, based on some of our previous experience with the partial splanchnic nerve sections above or below the diaphragm, that the technic of Smithwick will greatly improve the results of, and may even extend the indications for, operation. Most convincing proof is afforded by patients who have had a splanchnic nerve section done by one of the previous methods, with a return of blood pressure to a preoperative level, and who after undergoing a complete splanchnic resection show an excellent response. In our clinic the supradiaphragmatic and infradiaphragmatic nerve sections gave only

152. de Takáts, G.; Heyer, H., and Keeton, R. W.: The Surgical Approach to Hypertension, J. A. M. A., to be published.

153. Woods, W. W.: The Surgical Treatment of Hypertension, abstracted, Ann. Surg. **113**:1072 (June) 1941.

154. Smithwick, R. H.: A Technique for Splanchnic Resection for Hypertension, Surgery **7**:1 (Jan.) 1940.

temporary results, or none at all; since the technic of Smithwick has been adopted not only the patients with early and moderately advanced disease but those in group III, with retinal hemorrhages and detectable renal damage, have been improved. Whether the malignant phase is operable or not is still under debate.

A further extension of the surgical treatment to total sympathectomy has been reported by Grimson, Alving and Adams.[155] At present this operation seems unnecessarily radical. It may become the operation of choice if the Smithwick procedure will not maintain its efficiency in the five and ten year follow-up records. It is recognized by all surgeons interested in this field that, just as in evaluating results of operations for cancer, longer follow-up periods are necessary.

The marked symtomatic relief from headache, dizziness and palpitation in some patients who show no, or hardly any, reduction in the level of blood pressure has received a possible explanation through the work of Heinbecker.[156] He states that in over 70 per cent of surgically treated patients, symtomatic relief is obtained, which he explains on the basis of adrenal denervation. In animal experiments he was able to show that the pressor substance produced by the ischemic kidney sensitizes the vessels to epinephrine and that when the secretion of epinephrine is decreased this reaction is diminished. In addition, he makes the point that the role of the surgeon in the problem of hypertension is to determine whether and in what type of cases renal-adrenal denervation will effect a permanent drop in blood pressure and restore renal circulation to normal. Splanchnic nerve section on human beings showed a reduction of blood pressure to normal when nervous influences are initiating the train of events that lead to a permanent organic phase of the disease; the operation will not lower blood pressure appreciably once the renal ischemia is affected by mechanisms not under nerve control.

We must take exception to this last statement; for several years we have taken specimens of renal tissue for biopsy while performing sections of the splanchnic nerve and have found that patients who have marked structural damage following toxemia of pregnancy, eclampsia or rheumatic infection may still respond well to operation. It is true, however, that in this group the return of blood pressure to normal may take several months, indicating perhaps slowly progressive improvement in renal ischemia.

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155. Grimson, K. S.; Alving, A. S., and Adams, W.: Experimental and Clinical Basis for Total Bilateral Paravertebral Sympathectomy in Essential Hypertension, read at the meeting of the Central Society for Clinical Research, Chicago, Nov. 2, 1940.

156. Heinbecker, P.: Role for Surgeons in Problems of Essential Hypertension in Relation to Splanchnic Section, Ann. Surg. **112**:1101 (Dec.) 1940.

Cure of malignant hypertension in a child following nephrectomy is reported by Kennedy, Barker and Walters.[157] In a child of 7 years the removal of one kidney, which as a result of obstruction and infection had become atrophic, resulted in a return of blood pressure to normal. Before the operation the condition of the retina was characteristic of acute angiospastic retinitis. Shortly after the operation the changes in the ocular fundi were such that the ophthalmologist could state with confidence that complete recovery was assured.

Because of reports like these, the preoperative studies of hypertensive patients, especially the juvenile ones, should include a routine intravenous pyelogram. While some structural involvement of the other kidney may exist, the relief from hypertension may help its restitution. Late return of blood pressures to abnormal levels have been reported, however, and much interest is focused on five and ten year follow-up observations.

The improvement of renal circulation by omental or muscle grafts to the kidney has been attempted by Bruger and Carter.[158] Through an anterior, transperitoneal approach, omentum is sutured into the posterior cut surface of the renal capsule; when muscle is used, the capsule is stripped and the quadratus lumborum and psoas muscles are sewn into its place. Six of 9 patients operated on were relieved of their symptoms for two to eleven months. Headaches and vertigo had been especially striking in 4 of them. No measurable improvement of renal function was observed in any of these patients.

A similar negative result of renal grafts has been reported by two of us[159] (G. de T. and G. W. S.). We believed that incisions into the cortex of the kidney might help to establish vascular connections. Since the publication of our results, however, 1 of the patients, suffering from malignant hypertension with marked papilledema, has survived a five year period and is now free of symptoms and has no papilledema. Three additional patients have since had muscle implants into the kidney, in addition to a splanchnic nerve section. Histologic and dye injection studies would indicate that at least tubular circulation can be improved by these grafts. The combination of splanchnic nerve section with slender muscle grafts deeply implanted into renal parenchyma is now reserved for patients with more advanced renal damage.

157. Kennedy, R. L. J.; Barker, N. W., and Walters, W.: Malignant Hypertension in a Child: Cure Following Nephrectomy, Am. J. Dis. Child. **61**:128 (Jan.) 1941.

158. Bruger, M., and Carter, R. F.: Nephro-omentopexy and Nephromyopexy in the Treatment of Arterial Disease, Ann. Surg. **113**:381 (March) 1941.

159. de Takáts, G., and Scupham, G. W.: Revascularization of the Ischemic Kidney, Arch. Surg. **41**:1394 (Dec.) 1940.

AMPUTATIONS

Atlas [160] discusses the management of arteriosclerotic gangrene. He decries the recently created impression that gangrene is amenable to various forms of "conservative" therapy. This cannot be so because of the basic pathologic changes in the disease which affect the toes through occlusion of the digital arteries. These are end arteries, and there is little chance for rapid development of an effective collateral circulation. Conservative treatment should be considered when (1) the gangrenous process is localized to a single toe, (2) the gangrenous process is well demarcated with no tendency to spread, (3) there is no constitutional evidence of toxic absorption and (4) there is no cellulitis, osteomyelitis or lymphangitis. Conservative treatment consists of a prophylactic dose of gas and tetanus bacillus antitoxin on admission. Complete rest in bed is enforced, the leg being kept on a level lower than that of the heart. A cradle without light bulbs is used to protect the foot, and the gangrenous toe is kept scrupulously clean and protected by sterile dressings saturated with azochloramid or a suspension of zinc peroxide in sterile distilled water. Whisky is used as a vasodilating drug, and 100 cc. of a 5 per cent solution of sodium chloride is given intravenously every other day. When a gangrenous part is detached from the foot passive vascular exercise is started.

The operation of choice is the circular amputation through the lower third of the thigh, with primary closure. In the event of cellulitis or lymphangitis, a simple guillotine section through the upper third of the leg with the stump left open is rapidly performed under anesthesia. The open stump is treated with zinc peroxide. Sulfanilamide, high voltage roentgen radiation for gas bacillus infection and small blood transfusions are used when indicated. Later, when the risk of infection has abated, necessary stump revisions or reamputation at a higher level may be done. The danger of an infected amputation stump is that of septic pulmonary emboli. Ligation of the femoral vein just distal to the entrance of the saphenous vein at the time of amputation has lowered the mortality rate (Veal).

In a series of 28 patients with arteriosclerotic and diabetic gangrene Bowers and Kennedy [161] reported major amputations in 70 per cent, without a single death. The authors' patients were unselected, but close cooperation between internist and surgeon was maintained. The high mortality, in their opinion, is partially due to the fact that the patient is incorrectly prepared. No major amputation was done when the

160. Atlas, L. N.: Arteriosclerotic Gangrene: Major Clinical Problem, Am. J. Surg. **49**:467 (Sept.) 1940.

161. Bowers, W. F., and Kennedy, J. C.: Improved Management of Gangrene of the Foot, Am. J. Surg. **50**:573 (Dec.) 1940.

temperature of the patient was over 100 F. To lower the temperature and pulse in any case of gangrene of the foot in which major amputation is necessary, the patient is taken to the operating room and after general anesthesia is induced (cyclopropane by inhalation or pentothal sodium by intravenous injection) all necrotic tissue is removed by sharp dissection until a flat bleeding wound is produced. This débridement may include one or more digits and metatarsal bones and all overhanging soft tissues. The wound then is covered with a heavy layer of 40 per cent cod liver oil ointment, and a sterile dressing is applied. The temperature usually drops dramatically the next morning. Herein lies the danger, a tendency to allow time for self healing. This should not be done. The operative technic consists of a low thigh amputation, without use of a tourniquet to avoid a nonhealing stump or retractors, and severing of all tissues on the same level, since the blood supply goes superficially almost at right angles. Skin flaps are fashioned to avoid "dog ears" at each corner. The stump is closed tightly by means of interrupted silk sutures. A petrolatum strip is placed over the incision, and the stump is covered by a smooth, snug dressing (gauze roll, 5 yards [4.57 meters]). The stay in the hospital was reduced to sixteen days for the arteriosclerotic patients and twenty-five days for the diabetic patients who had been conservatively treated before amputation.

Samuels [162] repudiates as erroneous the assumption that diabetic gangrene with associated infection of the foot presupposes the extension of the infection throughout the entire extremity, particularly in the lymphatic vessels. He points out that if the urine of a patient cannot be made sugar free preoperatively with large doses of insulin an undrained infection of the foot is indicated and further medical treatment is a waste of time. Cyclopropane anesthesia is used. No tourniquet is provided. The procedure involves a supracondylar circular incision, the formation of flaps being avoided. This site is chosen because infection is almost always confined to the foot and also because thigh muscles are conserved and good length to the femur is preserved. By this technic the popliteal artery is found without difficulty, the sciatic nerve is not injected and no attempt is made to undermine tissues. Fine silk sutures are used to proximate the muscles and fasciae, and fine silk or silkworm gut is used on the skin. The patient is allowed out of bed the following day and in a wheel chair the second day. The sutures are removed on the sixth or seventh day. Amputation 8 inches (20.3 cm.) below the knee is attempted rarely, and only in those cases in which there is an oscillometric curve of 1.0 or more at the ankle level. The objections to this

162. Samuels, S. S.: Leg Amputations in Diabetic Gangrene, Ann. Surg. **112**: 105 (July) 1940.

procedure are the increased trauma necessary in the complicated dissection and poor protection for the end of the stump.

The three reviewed articles show sane conservatism in trying to save an extremity until it is useless, becomes intractably painful or endangers life. The mortality statistics are improving from year to year The report of Bowers and Kennedy is encouraging. They follow Zierold's suggestion of debriding the gangrenous extremity before doing a formal amputation. This method deserves further trial and may save many lives.

Gallie [163] summarized the experience of physicians in the Canadian army with amputations of the lower extremity as follows: Syme's amputation when well done is the best of all amputations. Amputation through the calf is suitable for men and women who have a good deal of leisure and who are not called on to stand for more than short periods. For men who are forced to earn their living on their feet the Gritti-Stokes amputation is better than either amputation below the knee or amputation through the middle of the thigh. Stumps of such amputations remained satisfactory for twenty years. Any amputation, with the exception of Syme's, is disabling and, in spite of the wonderful contributions made by the artificial limb maker, leaves a man seriously handicapped. It is unreasonable to expect him to compete on even terms in the general labor market. This difficulty can be minimized by training in some vocation in which loss of a leg is relatively unimportant.

The conclusions enumerated were based on experience with 2,448 amputations of the lower extremity, of which 746 were in the leg, 142 at the ankle and 1,468 above the knee.

In the discussion of Gallie's paper, Kirk,[164] of the United States Army, states that leg makers have not made suitable prostheses for the Syme amputation. He disagrees with Gallie in regard to amputations below the knee, which he thinks often give good side-bearing stumps. Instead of the Gritti-Stokes procedure, he favors a plastic supracondylar amputation.

The importance of closer cooperation between surgeons and artificial limb makers is obvious. The Council on Physical Therapy of the American Medical Association has created a committee which is issuing its recommendations in current numbers of THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION. This material will be reprinted in book form. Medical preparedness certainly requires a few simple directions along this line.

163. Gallie, W. E.: The Experience of the Canadian Army and Pensions Board with Amputations of the Lower Extremity, Ann. Surg. **113**:925 (June) 1941.

164. Kirk, N. T., in discussion on Gallie.[163]

News and Comment

Association of Military Surgeons of the United States.—The annual meeting of the Association of Military Surgeons of the United States will be held Oct. 29 to Nov. 1, 1941, at the Brown Hotel, Louisville, Ky. All members of the medical profession are invited to attend as guests, particularly members of the medical defense committees.

War medicine and surgery have changed considerably since the previous emergency. Mechanization of armies and air bombardments have created new and difficult problems in traumatic surgery and methods of treatments of wounds and extreme abrasions. The session will conclude with a mass review of military medicine and an inspection of Fort Knox.

The preliminary program of professional sessions of the meeting follows:

Col. Harold D. Corbusier, Medical Reserve, United States Army: Presidential Address.

Rear Adm. Ross T. McIntire, Surgeon General of the United States Navy: "Policies and Activities of the Medical Department of the United States Navy in the Present National Emergency."

Dr. Warren F. Draper, Assistant to the Surgeon General, United States Public Health Service: "Present Policies and Activities of the United States Public Health Service."

Brig. Gen. Frank T. Hines, Administrator of Veterans' Affairs: "Progress of the Part the Veterans' Administration Is Playing in the National Defense Program."

Major Frank B. Wakeman, Medical Corps, United States Army, representing Major Gen. James C. Magee, Surgeon General, United States Army: "Present Policies and Activities of the Medical Department of the United States Army."

Col. Robert H. Duenner, Medical Corps, United States Army, Fort Knox, Ky.: "Medical Service of the Mechanized Forces."

Col. Paul E. Howe, Sanitary Corps, United States Army: "Nutritional Problems of the Army."

Col. Fred H. Albee, Medical Reserve, United States Army: "Treatment of Ununited Fractures of Importance to the Military Service."

Capt. Lucius W. Johnson, Medical Corps, United States Navy: "Medical Service at Remote Naval Bases."

Capt. William L. Mann Jr., Medical Corps, United States Navy: "Medical Arrangements for Combined Operations of Land Forces and Sea Forces" (with motion pictures).

Papers are scheduled from the following speakers, but the titles are not yet available:

Major Gen. C. R. Reynolds, United States Army Ret.

Brig. Gen. Leigh C. Fairbank, Assistant to the Surgeon General, United States Army.

Col. Irvin Abell, of Louisville, Ky.

Col. Leonard C. Rowntree, Medical Reserve, United States Army; Chief, Medical Division, Selective Service System, Washington, D. C.

Col. Raymond A. Kelser, Veterinary Corps, United States Army.

Lieut. Col. David N. W. Grant, Medical Corps, United States Army, Office of the Chief of the Air Corps.

Book Reviews

Vitamin K. By H. R. Butt, M.D., Instructor of Medicine, Mayo Foundation, University of Minnesota, and A. M. Snell, Professor of Medicine, Mayo Foundation, University of Minnesota. Price, $3.50. Pp. x + 172, with 39 illustrations and 14 tables. Philadelphia: W. B. Saunders Company, 1941.

Vitamin K is one of those substances which from time to time appear in medicine suddenly, entering the field with a fine flourish and performing in such a spectacular fashion that for a time they come to occupy the center of the stage. Vitamin K was found unobstrusively. The original papers describing its usefulness in the treatment of a scurvy-like disease of chicks were published between 1929 and 1934. As so often happens, several years lapsed before clinicians realized the possible implications for human beings of a deficiency disease in chicks characterized by easy bleeding and relievable by a fat-soluble vitamin occurring in hog liver, hemp seed and certain cereals and vegetables. But in 1938 three independent papers drew attention to the fact that what was termed vitamin K had definite usefulness in overcoming the bleeding tendency encountered in cases of obstructive jaundice. Subsequently there has sprouted up a voluminous literature on vitamin K and substances with like effects. As a result new methods for studying diseases of the blood have been developed, new therapeutic weapons have been forged and a new chapter in medical discovery has been opened.

The authors of this small volume have done justice to their subject. They write well and modestly. They give all possible credit to Henrik Dam and his co-workers for the original discoveries. They do not lay undue emphasis on the fact that in the Mayo Clinic vitamin K was used for clinical work as early as anywhere. They review intelligently some 350 papers, putting in its proper relation to the total present knowledge of vitamin K what each one of these papers has added. On the whole, they give the history of vitamin K as it should be given. It is a dramatic story, told tersely and pungently and properly illustrated, and shows what an amazing substance this vitamin really is.

The Medical Aspects of Boxing. By Ernst Jokl. Pp. 251, with 54 illustrations. Pretoria, Union of South Africa: J. L. Van Schaik, Ltd., 1941.

This is an extraordinary book, since the writer has assembled not only an immense amount of information on the pathologic aspects of pugilism but a most interesting collection of the curiosa of boxing. It is a mine of useful material for the neurosurgeon, the athletic director and the industrial surgeon. The historical allusions and the interesting illustrations add to the readableness of the book. Perhaps most important of all is the proof that boxing should not be allowed in the air force, since even mild blows on the head may impair the sensitiveness of reflexes necessary in military aviation.

A Diabetic Manual. By Elliott P. Joslin, M.D. Seventh edition. Price, $2. Pp. 238, with 53 illustrations and 24 tables. Philadelphia: Lea and Febiger, 1941.

To Dr. Joslin diabetes has always been a challenge. It is mainly this spirit of combat with and triumph over the disease running through his book that differentiates it from other manuals for the diabetic patient, and surely the new recruit will be cheered by the snapshots of previous patients "before and after." Everything the diabetic person needs to know is there, even if the epigrammatic style is a little tiring to the reader who goes straight through the book. Unfortunately, through the country in general there are still many physicians too ignorant or too lazy to take advantage of the newer knowledge of diabetes and many patients too apathetic to cooperate.